CB 15/82/01

NCI/ICRDB/CB15 82/01

PB82-932001

ICRDB CANCERGRAM

INTERNATIONAL CANCER RESEARCH DATA BANK

IMMUNOBIOLOGY AND CANCER

Functional Aspects of Cellular Immunity

SERIES CB15 No. 82/01

JANUARY, 1982

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In this issue:

- EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS 1-50
- EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS 51-67
- EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION 68-90
- THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE 91-105
- ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY 106-107
- RELATED BIOLOGY OF IMMUNE CELLS 108-109
- CMI METHODOLOGY 110
- SUPPRESSOR CELL ACTIVITY 111

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. IMMUNOLOGICAL STUDY OF GASTRIC CANCER PATIENTS AMONG ATOMIC-BOMB (A-BOMB) SURVIVORS. II. IMMUNOLOGICAL STATUS IN POSTOPERATIVE PATIENTS.

Yamada Y, Tani T, Yanagawa E, Nakano A, Nakanashi K, Toge T, Niimoto M, Hattori T
Dept. Surgery, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi, Hiroshima 734, Japan
Hiroshima Igaku; 34(1):71-75 1981

The purified protein derivative (PPD) skin reaction, phytohemagglutinin (PHA) skin reaction, Ig and peripheral blood lymphocyte blastogenic (LB) reaction were determined before and 1 mo and 3 mo after surgery on gastric cancer patients who had or had not been exposed to the A-bomb explosion, and changes in these immunological parameters after surgery were determined separately for the patients with stage I + II and III + IV cancer according to the General Rules for the Gastric Cancer Study in Surgery and Pathology. The value of PPD skin reaction for stage I-II unexposed patients before, 1 mo after and 3 mo after surgery was 40.0 +-24.8, 28.9 +-18.1 and 32.8 +-25.1 mm, respectively; that for those exposed was 30.6 +-27.8, 22.6 +-20.7 and 23.4 +-17.4 mm, respectively. The value of PPD skin reaction for stage III-IV unexposed patients was 24.9 +-21.7, 18.9 +-20.7 and 19.4 +-19.2 mm, respectively; that for those exposed was 23.8 +-26.8, 14.4 +-16.8 and 22.0 +-26.8 mm, respectively. The value of PHA skin reaction for stage I-II unexposed patients was 81.7 +-33.6, 54.9 +-31.9 and 35.3 +-23.5 mm, respectively; that for the exposed patients was 74.1 +-32.2, 62.7 +-28.0 and 12.0 mm, respectively. That for stage III-IV unexposed patients was 59.7 +-29.4, 44.6 +-24.4 and 38.4 +-27.5 mm, respectively; that for exposed patients was 58.1 +-29.3, 34.1 +-18.0 and 37.3 +-32.1 mm, respectively. The serum Ig of exposed and unexposed patients was similar and the postoperative values were within the normal range. The value of PHA-LB reaction for stage I-II unexposed patients was 24,039 +-10,483, 14,420 +-7,262 and 25,125 +-10,285 cpm, respectively. That for stage III-IV unexposed patients was 20,962 +-9,276, 18,255 +-10,672 and 16,902 +-7,474 cpm, respectively. The value of pokeweed mitogen LB reaction was similar to that stimulated by PHA skin reaction. All immunological parameters showed similar values for both exposed and unexposed patients, no effect of the exposure on the postoperative recovery of the immunopotential being detected. (10 Refs) (In JPN)

2. A HISTOLOGICAL STUDY OF THE IMMUNE REACTION OF ADVANCED UTERINE CERVICAL CARCINOMA WITH REGARD TO THE EFFECT OF LOW-DOSE IRRADIATION AND PS-K.

Tsukahara Y, Shiozawa I, Sakai Y, Ishii J, Iwai S, Fukuta T
Dept. Obstetrics and Gynecology, Faculty Medicine, Shinshu Univ., Matsumoto-shi, Nagano Pref. 390, Japan
Nippon Sanka Fujinka Gakkai Zasshi; 33(2):279-284 1981

Histopathological studies were carried out to determine whether or not an immunological reaction was involved in the treatment of 144 cases of advanced cervical carcinoma. These patients had been subjected to radical hysterectomy. They were divided into three groups on the basis of the treatment performed. Thirty-two patients of them had undergone a radical operation only, 66 had operation after initial irradiation with a total dose of 1,000 rads and 46 were given po a daily dose of 6 g of PS-K over a period from 5 days prior to preoperative irradiation with 1,000 rads of telecobalt to one day before the radical surgery. The following conclusions could be drawn. Low-dose irradiation on the primary cancer-nest intensified the interstitial reaction. When PS-K was administered after low-dose irradiation, the interstitial reaction was intensified more remarkably than with irradiation alone. Moreover, it was possible for PS-K administration to restore the responsiveness of lymph nodes which had been inhibited by irradiation. Some of the observed morphological changes suggested the local occurrence of an immunological reaction. The following findings were made: (a) In the primary lesion of the uterine cervix, exudative cells consisting mainly of lymphocytes, plasma cells, and macrophages formed a barrier-like layer surrounding the cancer nest. Granulomata accompanied by foreign-body type giant cells were formed in the interstitial tissue. Moreover, lymphoid tissues with a germinal center were formed. (b) In the lymph nodes of the region involved, responsiveness was enhanced in the paracortical area, or a germinal center formed with its responsiveness enhanced. There was a correlation between the degree of interstitial reaction of the primary lesion and the survival results of a follow-up survey. There was also a correlation between the degree of enlargement of lymph nodes and the survival results of this survey. (9 Refs) (In JPN)

3. EARLY CHANGES IN PHOSPHATIDYLCHOLINE METABOLISM IN HUMAN ACUTE PROMYELOCYTIC LEUKEMIA CELLS STIMULATED TO DIFFERENTIATE BY PHORBOL ESTER.

Cassileth PA, Suholet D, Cooper RA
Hosp. Univ. Pennsylvania, Philadelphia, PA, 19104
Blood; 58(2):237-243 1981

The HL-60 leukemia cell line derived from a human acute promyelocytic leukemia is stimulated to differentiate into macrophages within 24-48 hr after exposure to the phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA). We studied early alterations (within 90 min of exposure to TPA) in phosphatidylcholine metabolism in HL-60 cells and found that phosphatidylcholine synthesis by methylation of phosphatidylethanolamine was inhibited in a dose-dependent fashion. In contrast, synthesis of phosphatidylcholine from endogenous choline was enhanced and correlated inversely with the degree of inhibition of the methylation pathway. Phorbol ester congeners of TPA caused similar alterations in phosphatidylcholine metabolism in direct relationship to their capacity to induce differentiation in HL-60 cells. Perturbation of phosphatidylcholine metabolism is an early membrane event in TPA-induced HL-60 cell differentiation. (Author abstract) (44 Refs)

4. TREATMENT OF GRAFT-VERSUS-HOST DISEASE IN HUMAN ALLOGENEIC MARROW GRAFT RECIPIENTS: A RANDOMIZED TRIAL COMPARING ANTITHYMOCYTE GLOBULIN AND CORTICOSTEROIDS.

Doney KC, Weiden PL, Storb R, Thomas ED
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Am J Hematol; 11(1):1-8 1981

This prospective randomized trial compared the effect of antihuman thymocyte globulin (ATG) vs corticosteroids as treatment of graft-vs-host disease (GVHD) in recipients of HLA-identical allogeneic bone marrow transplants. Patients undergoing transplantation as therapy for either hematologic malignancies or aplastic anemia were given methotrexate as postgrafting immunosuppression. Patients who nevertheless developed acute GVHD of moderate severity were randomized to receive either corticosteroid therapy or ATG therapy. Thirty-seven patients were randomized: 20 patients received corticosteroids, and 17 received ATG. Both ATG and corticosteroids were in general well tolerated, although all patients receiving ATG developed fever and chills. Both treatment modalities were associated with a mild decrease in severity of GVHD after therapy. There was, however, no significant difference between treatment groups, whether assessed by improvement in specific organ involvement, improvement in the overall grade of GVHD, need for additional therapy for acute GVHD, or the proportion of patients who developed chronic GVHD. Infectious complications and survival were also not different between treatment groups. Thus, corticosteroids were as effective as ATG for the treatment of acute GVHD in recipients of HLA-identical marrow transplants and, therefore, appear to be a reasonable choice as primary therapy for acute GVHD. (Author abstract) (21 Refs)

5. T AND B LYMPHOCYTES IN CARCINOMA OF PALATE.

Krishnamachary PA, Kesari G, Gangadhar Rao M, Reddy CR
Andhra Medical Coll., Visakhaptanam, India
Indian J Cancer; 18(2):108-111 1981

The T and B lymphocyte levels in the peripheral blood of 10 patients with carcinoma of the palate were compared with those of 20 normal healthy controls. There was no significant difference between the controls and the pretreatment levels of the absolute lymphocyte count. Immediately after radiotherapy the count fell and returned to normal values a few mo after completion of radiotherapy. The total T lymphocyte values in patients with carcinoma were lower than the control group and fell further immediately after radiotherapy. These values rose thereafter, but never reached control values. In carcinoma patients the absolute active T lymphocyte values were significantly lower than the control group, they rose after treatment, but never reached control levels. No significant variation in absolute B lymphocyte levels were noted between carcinoma patients and controls and between pretreatment groups and posttreatment groups. Patients with improved immunologic status after treatment had a better prognosis than those with a persistent poor immunological status. (20 Refs)

6. INVESTIGATIONS OF UNSPECIFIC IMMUNE REACTIVITY IN PATIENTS WITH HEAD AND NECK CARCINOMA.

Bier J, Nicklisch U
Abteilung fur Kiefer- und Plastische Gesichtschirurgie,, Universitatsklinikum Steglitz Freie Universitat Berlin, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany
Arch Otorhinolaryngol (NY); 232(2):145-163 1981

Nonspecific immune reactions in thirty patients with squamous cell carcinoma of the head and neck were compared with reactions in thirty healthy controls. Patients included 15 males and 15 females, aged 27-81 yr, with an av age of 59 yr. In vitro assays measured the blastogenic stimulation of lymphocytes by the mitogens phytohemagglutinin (PHA), Concanavalin A (ConA), and pokeweed mitogen (PWM). Absolute and percentage values for T-rosette-forming lymphocytes were obtained. Delayed hypersensitivity to dinitrochlorobenzene (DNCB) was measured by skin tests. Parameters were determined in patients at 4-wk intervals for a period of 1 yr or until death. Patients were treated by surgery, chemotherapy with Bleomycin and Methotrexate, and radiation therapy. Follow-up continued for 5 yr. Tumor patients before treatment showed marked reduction of immune response, when compared to controls. A further, temporary reduction occurred during treatment. No correlation could be demonstrated between tumor stage and nonspecific immune reactivity. No useful statement could be made regarding nonspecific immune reactivity in patients with squamous cell carcinoma of the head and neck. (37 Refs) (In GER)

7. MULTIVARIATE ANALYSIS OF T-CELL FUNCTIONAL DEFECTS AND CIRCULATING SERUM FACTORS IN HODGKIN'S DISEASE.

Schulof RS, Bockman RS, Garofalo JA, Cirrincione C, Cunningham-Rundles S, Fernandes G, Day NK, Pinsky CM, Incefy GS, Thaler HT, Good RA, Gupta S
Dept. Medicine, Div. Hematology and Oncology, George Washington Univ. Sch. Medicine, 2150 Pennsylvania Ave., N.W., Washington, DC, 20037
Cancer; 48(4):964-973 1981

A comprehensive immunologic and serologic analysis was performed on 31 untreated patients with Hodgkin's disease. Immune evaluations stressed T-cell functional activity and included traditional parameters (PHA responsiveness and delayed hypersensitivity skin reactivity), as well as newer functional assays [T-cell colony formation, chemotaxis, spontaneous and antibody-dependent cytotoxicity, and concanavalin A-induced suppressor cell activity (CISA)]. Serum factors included ferritin, prostaglandins, zinc, copper, immune complexes, and thymic hormone activity. Every patient exhibited at least one T-cell or serum abnormality. The greatest percentage of patients exhibited T-cell defects in chemotaxis (85%), colony formation (81%), and PHA reactivity (64%). Immune defects were more common with advanced disease but were not related to absolute T-cell or monocyte count, skin test anergy, or abnormalities of Tmu/Tgamma cell proportions. Linear relationships were identified among abnormalities in the three assays employing mononuclear cells (PHA, colony formation, CISA) which may have reflected the inhibitory influence of monocytes present in the mononuclear cell preparations. Low serum zinc correlated with marked impairment of T-cell chemotaxis. Elevated prostaglandins were associated with high PHA reactivity and with depressed colony formation. Elevated prostaglandins were associated with high PHA reactivity and with depressed colony formation. Our results indicate that many complex factors, including intrinsic T-cell defects, contribute to the impaired immunity associated with Hodgkin's disease. (Author abstract) (62 Refs)

8. T LYMPHOCYTE SUBPOPULATIONS IN THE BONE MARROW AND PERIPHERAL BLOOD OF UNTREATED PATIENTS WITH MYELOMA.

Giustolisi R, Guglielmo P, Rizzo M, Cacciola E
Cattedra di Ematologia, Universita degli Studi di Catania, Via S. Citelli, 95124 Catania, Italy
Ric Clin Lab; 11(2):129-137 1981

T lymphocyte populations were studied in the bone marrow and the peripheral blood of 10 untreated patients (9 men, 1 woman; 50-75 yr old) with multiple myeloma. Total E rosette-forming cell (ERFC) count in the bone marrow was within a normal range in 9/10 patients, while the peripheral blood ERFC was reduced in 9/10. There was a significant decrease of 'high-affinity' (Tha) ERFC in both bone marrow and peripheral blood; 'low-affinity' (Tla) ERFC showed a significant increase in the bone marrow and no changes (compared with control values) in the peripheral blood. These findings indicate that the increase in the Tla (putative suppressor T cells) was absolute in the bone marrow whereas it was relative in the peripheral blood because of a decrease in the Tha level. (36 Refs)

9. NATURAL CYTOTOXICITY OF PERIPHERAL BLOOD LYMPHOCYTES AND REGIONAL LYMPH NODE CELLS IN BREAST CANCER IN WOMEN.

Cunningham-Rundles S, Filippa DA, Braun DW, Antonelli P, Ashikari H

Clinical Immunology and Tissue Typing Lab., Memorial Sloan-Kettering Cancer Center, 1274 York Ave., New York, NY, 10021

JNCI; 67(3):585-590 1981

Natural cytotoxicity was studied before surgery or other treatment in 83 women with primary, untreated breast cancer. Peripheral blood lymphocytes (PBL) and cytotoxicity of regional lymph node cell(s) (RLNC) were examined in a 4-hr 51Cr release assay against the target cell K-562. Results indicated that greater than one-third of breast cancer patients have more negative lymphocyte cytotoxic activity toward K-562 than do the other two-thirds. Similar results were observed for PBL of 25 patients found to have benign breast lesions. Of these patients, 23 had fibrocystic disease. The difference between these findings and findings with normal control lymphocytes studied in parallel was highly significant (p less than 0.001). The study of RLNC cytotoxicity in patients with breast cancer showed that 25% of the patients' RLNC had significant natural cytotoxic activity toward K-562. Incubation of RLNC with interferon in vitro before addition of labeled K-562 cells did not induce cytotoxicity in RLNC that did not have this activity initially. (Author abstract) (23 Refs)

10. TRANSPLANTATION FOR ACUTE LEUKAEMIA WITH HLA-A AND B NONIDENTICAL PARENTAL MARROW CELLS FRACTIONATED WITH SOYBEAN AGGLUTININ AND SHEEP RED BLOOD CELLS.

Reisner Y, Kirkpatrick D, Dupont B, Kapoor N, Pollack MS, Good RA, O'Reilly RJ

Memorial Sloan-Kettering Cancer Center, Box 380, 1275 York Ave., New York, NY, 10021

Lancet; 2(8242):327-331 1981

A new procedure for enrichment of marrow precursors and removal of T lymphocytes from large vol of human bone marrow, involving initial differential agglutination of T lymphocytes and mature marrow elements with soybean agglutinin, followed by rosetting with sheep RBCs, was used to fractionate marrow cells from an HLA-A, B, DR non-identical, MLC non-reactive, paternal donor for transplantation into an infant with acute leukemia. This transplant became completely engrafted and resulted in full recovery of normal, donor-derived hematopoietic function without graft-versus-host disease, sustained for 11 wk after transplantation, at which time the patient's leukemia recurred. Subsequently, the patient received chemotherapy and achieved a remission with regeneration of normal marrow cells of donor origin. The patient's course demonstrated the potential of lectin-separated marrow grafts to restore durable hematopoiesis, without graft-versus-host disease, in a lethally irradiated allogeneic host. (Author abstract) (23 Refs)

11. IMMUNOLOGICAL STATUS OF THE PATIENTS WITH LARYNGEAL NEOPLASMS AND SOME ASPECTS OF NONSPECIFIC IMMUNOTHERAPY.

Nasretdinov TK, Gorodilova VV, Pogosov VS, Akopian RG
Dept. Otorhinolaryngology, Central Inst. Advanced Training for Physicians, Moscow, USSR
Vestn Otorinolaringol; (4):56-61 1981

The indices of humoral and cellular immunity were studied in 212 patients with laryngeal neoplasms. There was a stage-dependent decrease of the bactericidal and complement activity of the blood serum as well as a decrease of lysozyme level. The frequency of positive hypersensitivity reaction of the delayed type to dinitrochlorobenzene in untreated patients with laryngeal neoplasms was significantly lower than that in healthy controls. Of 212 patients, 72 received postoperative nonspecific immunotherapy. Immunostimulation resulted in a gradual normalization of the natural, cellular and humoral immunity. (37 Refs) (In RUS)

12. NATURAL ANTIBODIES TO THE HUMAN T CELL LYMPHOMA VIRUS IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA.

Posner LE, Robert-Guroff M, Kalyanaraman VS, Poiesz BJ, Ruscetti FW, Fossieck B, Bunn PA, Minna JD, Gallo RC
Lab. Tumor Cell Biology, NIH, Bethesda, MD, 20205
J Exp Med; 154(2):333-346 1981

Serum samples were obtained from patients with cutaneous T cell lymphoma (CTCL) and leukemia, and from 55 normal random donors. Retroviruses HTLV-CR (grown in HUT 102 cells) and HTLV-MB, isolated from patients CR and MB, respectively, were used, along with several other retroviruses. The sera were screened for the presence of natural antibody to HTLV-CR, using a solid-phase radioimmunoassay. Sera from patient CR and one other patient reacted specifically with proteins of HTLV-CR. CR serum also reacted with HTLV-MB proteins. Solid-phase immunocompetition and competition radioimmunoprecipitation assays demonstrated the specificity for HTLV-CR proteins. Patient CR antibodies were directed against viral core proteins with mol wt of 24,000 and 19,000, as shown by radioimmunoprecipitation analysis. Some reactivities to other animal retroviruses, including the baboon endogenous virus, simian sarcoma virus, feline leukemia virus, and gibbon ape leukemia virus, were demonstrated. These reactivities apparently were not virus-specific, but related to cellular antigen contamination of viral preparations or to antigens in fetal calf serum. The results indicate for the first time a specific antibody reaction to a retrovirus in humans. (38 Refs)

13. SERUM COMPLEMENT LEVELS IN UTERINE CERVICAL CANCER PATIENTS AND THEIR RELATIONSHIP TO CELL-MEDIATED IMMUNITY.

Gojobori M, Mashiba H, Matsunaga K, Jimi S
(c/o Mashiba) Div. Immunology, Natl. Kyushu Cancer Center, 595 Notame Minami-ku, Fukuoka 815, Japan
Jpn J Clin Oncol; 11(1):101-107 1981

Complement (C) levels were examined in uterine cervical cancer patients in relation to disease progression and various parameters of cell-mediated immune response. The reason for the elevated levels of C in cancer patients is discussed. The mean C3 concentration in serum of healthy controls and in patients before therapy in Stages 0, I, II, III, and IV was 101.6, 109.4, 138.5, 123.9, 144.2, and 117.5 mg/deciliter (dl), respectively. The mean C4 concentration in serum of healthy controls and in patients in Stages 0, I, II, III, and IV was 10.5, 21.5, 24.8, 15.6, and 21.8 mg/dl, respectively. The majority of healthy controls possessed low levels of C3, less than 120 ml/dl, and high responsiveness to phytohemagglutinin (PHA), while Stage I, II, and III patients generally showed high levels of C3 and a low response to PHA. However, 2/4 Stage IV patients showed low levels of C3 and a low response to PHA. No significant correlation between C3 concentration and lymphocyte response to PHA was observed. Healthy controls and Stage I patients showed a low degree of cytotoxicity while Stage II and III patients showed a high degree of activity. No correlation was noted between C3 concentration and cytotoxicity. Healthy controls showed low levels of lymphotoxin activity, while Stage I and II patients showed high levels of this activity. A significant correlation between C3 and lymphotoxin activity was observed. (38 Refs)

14. PRODUCTION OF AN ANTI-TUMOUR CYTOTOXIN BY HUMAN MONOCYTES.

Matthews N
Dept. Medical Microbiology, Welsh Natl. Sch. Medicine, Heath Park, Cardiff Cf4 4XN, Wales
Immunology; 44(1):135-142 1981

Human monocytes incubated in vitro for 20 hr at 37 C release a factor which is cytotoxic to a number of human and murine tumor cell lines: untransformed cells appear to be less susceptible. A similar factor is produced under comparable conditions by myelomonocytic leukemic cells and by macrophages derived from monocytes by in vitro culture for 8 days. Max production of the factor occurred in the presence of fetal calf serum or autologous plasma and endotoxin. The factor is newly synthesized in culture as its production is reduced if the monocytes are treated with cycloheximide or actinomycin D or incubated at lower temperatures. Freshly isolated monocytes do not release the factor on freeze-thaw or hypotonic lysis. The monocyte cytotoxin has apparent mol wt of 34,000 on Ultrogel AcA54 gel filtration and 140,000 on gradient polyacrylamide gel electrophoresis; it has beta2-gamma1 electrophoretic mobility in polyacrylamide gel and does not appear to be C3a or arginase. (Author abstract) (18 Refs)

15. NATURAL KILLER (NK) ACTIVITY OF NORMAL HUMAN PERIPHERAL BLOOD LYMPHOCYTES AGAINST ERYTHROLEUKEMIC CELL LINE K 562.

Tanaka Y
Dept. Pediatrics, Hiroshima Univ. Sch. Medicine, Hiroshima 734, Japan
Hiroshima J Med Sci; 30(2):115-126 1981

The NK activities of peripheral blood lymphocytes from healthy human adults and children were investigated with a 3-hr 51Cr release assay in which the K 562 erythroleukemic cell line was used. While the individual variation of cytotoxic activities was wide, individuals with high or low reactivity tended to maintain the same level of cytotoxic activity. Mononuclear WBC from cord blood had very little NK activity, but the level increased in infancy to the adult level. When red cells were added to the lymphocyte preparation, in a ratio of 10:1 or more, NK activity was significantly suppressed. Contaminating granulocytes, however, had no effect on NK activity. The NK activity of lymphocytes treated with Tris-buffered ammonium chloride was drastically reduced: such treatment should be avoided. When monocytes were removed, the cytotoxic activity against K 562 cells increased from 9.8% to 98.2% in 13/16 cases tested. The possibility of monocyte-NK cell interaction was discussed. Cryopreserved peripheral blood mononuclear WBC retained more than 80% of their NK activity. (55 Refs)

16. NATURAL KILLER (NK) ACTIVITY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Tanaka Y
Dept. Pediatrics, Hiroshima Univ. Sch. Medicine, Hiroshima 734, Japan
Hiroshima J Med Sci; 30(2):127-133 1981

The NK activity of peripheral blood mononuclear cells from 20 children (aged 1-13 yr) with acute lymphoblastic leukemia at the time of diagnosis and during chemotherapy was investigated. Before chemotherapy, in five children the NK activity increased with the effector to target cell (E/T) ratio; in three children the NK activity was within the normal range, and in two it was significantly lower. Bone marrow cells aspirated from iliac crests in these five patients showed no NK activity against K 562 target cells. NK activity decreased after the start of induction therapy with vincristine and prednisolone. After complete remission, NK activity returned to normal levels (higher than at the time of diagnosis in four patients). During maintenance chemotherapy, NK activity in 15 children with ALL in continuous complete remission was 44.9 +-16.9% compared with 40.8 +-11.5% in 20 healthy children and 41.3 +-14.2% in 26 healthy adults. (36 Refs)

17. IMPAIRED LEUKOCYTE MOBILITY AND PRODUCTION OF MONOCYTE-DERIVED GRANULOTACTIC FACTOR IN PEDIATRIC MALIGNANT DISEASE DURING CHEMOTHERAPY.

Tono-oka T, Nakayama M, Ohkawa M, Takeda T, Matsumoto S
Dept. Pediatrics, Hokkaido Univ. Sch. Medicine, Sapporo 060, Japan
Tohoku J Exp Med; 134(3):301-310 1981

An agarose plate method was used to evaluate the ability of granulocytes and monocytes to migrate spontaneously and to respond to chemotactic factor, and the ability of mononuclear cells (MNC) to produce derived chemotactic factor for granulocytes (CFG) in pediatric patients (17 aged 2-14 yr) with malignancies (7 acute lymphocytic leukemia (ALL), 5 acute myelocytic leukemia (AML), 4 neuroblastoma (NB), 1 rhabdomyosarcoma (RMS)). Chemotactic responses of all the granulocytes to bacterial chemotactic factor were within the normal range, while the chemotactic responses to zymosan activated serum were decreased in 11-17 occasions. Many patients with malignancies had decreased numbers of normal migrating monocytes during chemotherapy, while random mobility of granulocytes of all the patients was within the normal range. Since there was no difference in the degree of the impairment between patients in remission and those during induction chemotherapy, these impairments were attributed to induction by chemotherapeutic agents, which in turn, causes the susceptibility to bacterial infections observed in these patients. (23 Refs)

18. UNIQUE IMMUNOLOGIC PROBLEMS IN HUMAN BONE MARROW TRANSPLANT RECIPIENTS.

Storb R, Tsoi MS, Witherspoon RP, Sullivan K, Lum L, Deeg HJ, Atkinson K
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, W A, 98104
Transplant Proc; 13(3):1624-1627 1981

Three selected immunologic aspects of allogeneic ,arrpw grafting are discussed, including sensitization by preceding blood transfusions and marrow graft rejection, reconstitution of immunologic responsiveness, and graft-vs-host disease (GVHD) and graft-host tolerance. Rejection of the marrow graft and death from hemorrhage or infection have been a major compiication in patients with aplastic anemia, and has been related to pretransplant transfusions. Experimental evidence supporting this occurrence in monkeys and dogs is presented. In 30 patients who had not been transfused, graft failure was the exception, with 83% of the patients surviving between 1.5 and 8 yr. Patients without or with only transient GVHD subsequently recovered immunologic function, while those that had chronic GVHD remained immunologically deficient. Most tests and lymphocyte markers for immunologic parameters are not clinically relevant after marrow transplantation and the need for new approaches is emphasized. The use of detection of B- and T-cell defects and suppressor cells as an immunologic parameter is suggested. Evidence is presented that stable chimerism in man is maintained by 'specific' suppressor cells. Clinical application of these findings is discussed. (24 Refs)

19. TREATMENT OF DISSEMINATED MALIGNANT MELANOMA WITH HIGH-DOSE ORAL BCG.

Varella AD, Bandiera DC, De Amorim AR, Calvis LA, Santos IO, Escaleira N, Gentil F
Hospital A. C. Camargo Fundacao Antonio Prudente, Prudente, 211, 01509 Sao Paulo, SP, Brazil
Cancer; 48(6):1353-1362 1981

Thirty patients with unresectable disseminated melanoma (Stage IV) were treated with BCG (Moreau strain - Rio do Janeiro) by mouth, with weekly doses ranging between 200 mg and 28,000 mg. Five patients died in the first 2 mo of treatment. Of the remaining 25 patients, 2 (8%) showed complete regression, and 1 (4%) partial regression. Seven patients (28%) had stabilization of the disease for a 6-mo period, and 15 (60%) had progression of the disease. Complete and partial regressions were seen only in patients with extravisceral (sc) metastases, and were associated with a longer survival time. Regression of the sc metastatic nodules was always accompanied by the following local phenomena: increased temperature; local inflammation; softening, pain and pruritus at the nodule site; and a gradual decrease in size. At the site of the tumor mass, a hypochromic halo appeared. This halo remained permanently and was pathognomonic of the metastatic nodule rejection. When the halo was fully established, the inflammatory infiltrate was minimal and the malignant cells disappeared. If the area contained hairs, they underwent complete albinization. Serial biopsies of the nodules undergoing inflammatory changes and decreased consistency exhibited an intense cellular infiltration of lymphocytes, macrophages, and plasma cells around the malignant cells. This sometimes simulated lymphoid follicle formation involving the melanoma cells associated with necrosis in a centripetal way. Some patients with visceral metastases (particularly pulmonary) had an unexpectedly long survival, apparently associated with interruption of the growth rate of the masses. Eleven out of 20 deaths were due to cerebral metastases. When cerebral disease was diagnosed, BCG was discontinued and the administration of corticoids was usually associated with a disappearance of the inflammatory signs at the nodule sites, but with progression of the disease. Toxicity was minimal. (Author abstract) (37 Refs)

20. REASSESSMENT OF THE RELATIONSHIP BETWEEN ARYL HYDROCARBON HYDROXYLASE AND LUNG CANCER.

McLemore TL, Martin RR, Wray NP, Cantrell ET, Busbee DL
(c/o Busbee) Dept. Biology, Genetics Center, North Texas State Univ., Denton, TX, 76203
Cancer; 48(6):1438-1443 1981

Aryl hydrocarbon hydroxylase was measured in cultured human WBC induced with benzathracene and in pulmonary alveolar macrophages induced in situ in cigarette smokers. Considered separately, neither WBC AHH nor macrophage AHH levels were distinctly different in either noncancer or lung cancer patients. Considered simultaneously, WBC and macrophage AHH levels are quite different in noncancer and lung cancer patients. The lung cancer patient group was seen to contain a significantly higher percentage of persons with high levels of AHH than did an age-matched group of noncancer patients, (p less than 0.001), when more than one tissue was assayed to determine the individual's enzyme levels. (Author abstract) (42 Refs)

21. SPECIFIC RED CELL ADHERENCE TEST AND UNSPECIFIC IMMUNE RESPONSE IN PATIENTS WITH SUPERFICIAL BLADDER CANCER.

Jakse G, Hofstadter F, Mark R
Dept. Urology, Univ. Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria
Urol Int; 36(3):171-177 1981

ABH antigenicity and unspecific immune response were evaluated in 31 patients with superficial transitional cell carcinoma. Twenty six percent of these patients showed a reduced dinitrochlorobenzene (DNCB) reaction. There was no significant difference in the monocyte chemotaxis of patients with benign urological diseases and patients with superficial bladder cancer. However, a significant difference exists versus patients with deeply infiltrating carcinomas. Twenty patients revealed a loss of ABH antigens on the initial tumor. During the follow-up of at least 1 yr, patients with negative DNCB skin test, reduced monocyte chemotaxis and negative specific red cell adherence test demonstrated a high rate of recurrent tumors and in one of seven a progressive tumor developed. (Author abstract) (39 Refs)

22. GOLGI-ANAE POSITIVITY IN LEUKEMIC BLAST CELLS: A POSSIBLE T-SUPPRESSOR CELL LEUKEMIA.

Burgio VL, Maccario R, Re R, Ugazio AG
Instituto Patologia Medica I, Universita di Pavia, Policlinico S. Matteo, Piannale Golgi, 1-27100 Pavia, Italy
Acta Haematol (Basel); 66(2):122-126 1981

Different patterns of acid alpha-naphthyl-acetate esterase (ANAE) positivity in lymphocytes have been related to distinct functional lymphocyte subpopulations. A case of T-ALL with a cytochemical and immunological phenotype consistent with a T-suppressor cell leukemia is reported. In particular a specific pattern of Golgi-ANAE positivity is probably characteristic of TG cells, which include a subset with suppressor function. (Author abstract) (18 Refs)

23. ANTI-IA-REACTIVE CELLS IN MYCOSIS FUNGOIDES: A STUDY OF SKIN BIOPSIES, SINGLE EPIDERMAL CELLS AND CIRCULATING T LYMPHOCYTES.

Tjernlund UM, Scheynius A, Kabelitz D, Klareskog L
Dept. Dermatology, Univ. Hosp., S-750 14 Uppsala 14, Sweden
Acta Derm Venereol (Stockh); 61(4):291-301 1981

Skin sections, epidermal cells in suspension and circulating T lymphocytes were investigated for the presence of Ia-like antigens in a group of patients with the cutaneous T-cell lymphoma mycosis fungoides (MF) and in healthy controls. Highly purified anti-Ia antibodies were used in indirect immunofluorescence, indirect peroxidase and peroxidase-antiperoxidase techniques. Allogeneic and peroxidase-antiperoxidase techniques. Allogeneic and autologous mixed leukocyte reaction tests with epidermal cells from MF lesions as stimulator cells were also performed The majority of the dermal lymphohistiocytes and mononuclear cells in the epidermal Pautrier microabscesses expressed Ia-like antigens. So also did a greater proportion of circulating T lymphocytes than in the controls. In some MF patients a high percentage of single epidermal cells of non-lymphoid character also reacted with the antibodies. The possible significance of the present findings for the pathogenesis of MF is discussed. (Author abstract) (30 Refs)

24. NUTRITIONAL SUPPORT OF CANCER PATIENTS.

Faintuch J

Disc. Cir. Ap. Digestivo, Hospital das Clinicas da Faculdade de Medicina da Univ. da Sao Paulo, Sao Paulo, Brazil

Rev Hosp Clin Fac Med Sao Paulo; 36(2):41-43 1981

Studies on malnutrition and nutritional support in cancer patients are reviewed. Chemotherapy and radiotherapy may cause malnutrition due to toxic side-effects, such as nausea, emesis, gastritis, stomatitis, glossitis, diarrhea, hemorrhage from the digestive tract, loss of appetite, malabsorption, stenosis, rectocolitis, and dysphagia. Malnutrition in cancer patients is associated with therapy failure and increased mortality. Malnutrition and immune deficiency are reversed by realimentation in a considerable percentage of the patients. Whenever possible, nutritional rehabilitation should precede or ac company cancer therapy. The route of alimentation is irrelevant for the effect, even though some animal experiments show increased tumor rate during iv than oral alimentation. Nutritional support in cancer patients is unable to prolong the survival, but helps reduce the mortality in selected cases. (30 Refs) (In POR)

25. CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY OF GYNECOLOGIC TUMORS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank

ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205

Clinical Immunology and Immunotherapy of Gynecologic Tumors (Cancer Overview) Freedman, R S, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922802:; OT-81/02:52pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. The scope of this Overview includes all clinical aspects of the immunology and immunotherapy of gynecologic tumors. Immunologic studies of gestational trophoblastic disease include paternal antigen expression, human leukocyte antigen histocompatibility, and immunoassays of betaglycoprotein and human chorionic gonadotropin (HCG). Antigenic studies of the uterine cervix include herpes viruses, cytomegaloviruses, tumor-associated antigens, carcinoembryonic antigens and beta oncofetal antigens. Studies of cellular immune response, lymph node morphology and lymphocytic infiltration as prognostic indicators of the uterine cervix are covered as well as the effects of radiotherapy on the immune status of patients with cervical carcinoma. Immunologic aspects of ovarian tumors which are covered include human ovarian tumor-associated antigens and oncofetal antigens. Non-specific, active specific, and other immunotherapeutic trials in gynecologic neoplasms are also included in this Overview.

26. CAMP CONTENT IN T AND B LYMPHOCYTES IN PERIPHERAL BLOOD OF HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

Konopka L, Karpowicz M, Brodzki M, Pawleski S

Klinika Chorob Wewnetrznych, Instytut Hematologii AM, ul. Chocimska 5, 00-791 Warsaw, Poland

Pol Arch Med Wewn; 65(4):287-293 1981

The intracellular cyclic AMP (cAMP) levels were determined in isolated peripheral T and B lymphocytes from 12 healthy blood donors and 14 patients (8 men and 6 women, 33-75 yr old) with chronic lymphocytic leukemia. The intracellular cAMP levels (in picomole/10(7) cells) were 26.70 +-4.80 in the T cells and 43.30 +-6.30 in the B cells of the donors, and significantly decreased in the leukemia patients (12.50 in the T cells and 4.50 in the B cells). After excluding the five patients in clinical Stages 0 and I, the mean cAMP levels were even lower: 10.8 in the T cells and 4.90 in the B cells. The observed decrease in the intracellular cAMP concentrations in leukemic lymphocytes is attributed to immunological and functional immaturity of the B cells. (18 Refs) (In POL)

27. TRANSFER FACTOR AND DELAYED HYPERSENSITIVITY IN PATIENTS WITH SARCOIDOSIS.

Votava V, Haskovcova H, Strejcek J, Pekarek J

I. Klinika tuberkulozy a respiracnich nemoci, FVL UK, Katerinska 19, 120 00 Prague 2, Czechoslovakia

Stud Pneumol Phtiseol Cech; 41(5):338-342 1981

Transfer factor (TF) from cured sarcoidosis patients without clinical, radiological, and immunological signs of the disease and from healthy subjects with pronounced hypersensitivity to tuberculin was administered sc to patients with sarcoidosis. The subsequent in vitro tests (E rosette, spontaneous and phytohemagglutinin-stimulated blast transformation, and phagocytosis tests) showed a tendency to normalization of the formerly decreased parameters of cell-mediated immunity. TF from cured patients was more effective than that taken from healthy subjects. (9 Refs) (In CZE)

28. THE ROLE OF ANTIBODY IN TUMOR IMMUNITY.

Economou JS

Dept. Surgery, Center Health Sciences, Univ. California, Los Angeles, CA

Surg Gynecol Obstet; 153(3):417-431 1981

Antibody may sensitize tumor cells for destruction by nonimmune host effector elements that include complement, macrophages, lymphocytes, neutrophils, eosinophils or platelets. Small numbers of tumor cells may be very efficiently suppressed in vivo. Antibody immunotherapy can also be used successfully in combination with other modalities, such as chemotherapy, in the treatment of larger tumor burdens. Perhaps the greatest potential application of antibody in cancer therapy is its use as a tumor-specific delivery vehicle for cytotoxic substances. The opportunity to produce large quantities of monoclonal antibody, afforded by current hybridoma technology, will revolutionize the application of antibody to cancer medicine. (Author abstract) (211 Refs)

29. SEQUENTIAL COMBINATION CHEMOIMMUNOTHERAPY FOR VARIOUS MALIGNANT TUMORS: CLINICAL AND LABORATORY RESULTS.

Akiyoshi T, Kawaguchi M, Miyazaki S, Koba F, Tsuji H
Dept. Surgery, Res. Inst. Balneotherapeutics, Kyushu Univ., Beppu 874, Japan
Jpn J Surg; 11(4):283-290 1981

A new chemoimmunotherapy program was tested in 139 patients with various advanced malignant tumors. The program consisted of cyclophosphamide (200 mg, iv) on day 1, vibrio cholerae neuraminidase-treated autologous tumor cells admixed with BCG (id) on day 4, and mitomycin C (10-16 mg, iv) plus 5-fluorouracil (500 mg/iv) on day 7 of each course. Maintenance treatment with tegafur (600 mg, po) and immunostimulants was started on day 14. Ninety-nine patients were treated with one course of therapy followed by maintenance treatment for at least 6 mo; the remaining 40 patients received two to six courses at 1-to 6-mo intervals. Among the 65 evaluable patients, 14 (22%) had a favorable clinical response to the new regimen. Among patients with gastric carcinoma, survival was significantly longer in those receiving chemoimmunotherapy than in controls who received no adjuvant therapy. Cell-mediated immune response to autologous tumor extract was detected in 12/42 patients following therapy; immune reactivity measured by the PPD skin test and by phytohemagglutinin lymphocyte blastogenesis was slightly increased after treatment. Prognosis and post-therapy immune reactivity were significantly related, although there was no definite relationship between pretherapy skin reactivity and survival. The results suggest that immunocompetence may be essential to the effectiveness of this combination treatment. (14 Refs)

30. REGULATION OF GENE EXPRESSION BY TUMOR PROMOTERS. II. CONTROL OF CELL SHAPE AND DEVELOPMENTAL PROGRAMS FOR MACROPHAGES AND GRANULOCYTES IN HUMAN MYELOID LEUKEMIC CELLS.

Liebermann D, Hoffman-Liebermann B, Sachs L
Dept. Genetics, Weizmann Inst. Science, Rehovoth 76100, Israel
Int J Cancer; 28(3):285-291 1981

Regulation of the developmental programs for macrophages and granulocytes has been analyzed, using two-dimensional gel electrophoresis of the cytoplasmic protein changes, in a human myeloid leukemic cell line (HL60) that can be induced to differentiate to macrophages by the macrophage and granulocyte-inducing (MGI) protein and the tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA), and to granulocytes by dimethylsulfoxide (DMSO). Studies on the protein changes induced by the different inducers showed a similar developmental program for macrophage differentiation induced by MGI or TPA, which differed from the beginning from the granulocyte program induced by DMSO. Comparison with normal cells from human peripheral blood has shown that the developmental programs induced in the HL60 cells are relevant to the normal programs of differentiation for these two cell types. Unlike MGI and DMSO, TPA induces rapid attachment of the HL60 cells to the surface of the Petri dish. Combined treatment with TPA and DMSO showed cell attachment, extensive spreading of the cells, the regulation of specific proteins and expression of the macrophage program. The addition of TPA to cells induced for the granulocyte program by DMSO resulted in cell attachment and spreading and a switch-over from the granulocyte to the macrophage program. The results indicate that cells in suspension can express either the macrophage or granulocyte program depending on the inducer, and that changes in cell shape associated with cell attachment induced by TPA can regulate specific proteins and restrict the developmental program to macrophages. It is suggested that the in vivo environment of cells in relation to the possibilities for cell adhesion, which can be regulated by tumor promotors, may play a major role in determining the developmental program of myeloid and other cell types. (Author abstract) (41 Refs)

31. A NEW LOOK AT MALIGNANT LYMPHOMAS.

Parker JW

Sch. Medicine, Univ. Southern California, Los Angeles, CA

Diagn Med; 4(4):77-80,85,87-90,92,94,96,98-100,103-105,108,110,113 1981

A general review is presented of malignant lymphomas (ML), the diagnosis and treatment of which has greatly improved in the last 10 yr. The classification of ML as either lymphocytic or histiocytic is being reconsidered today in light of our new understanding that the immune system consists of three major compartments: T and B lymphocytes, and histiocytes/macrophages and that malignant cells can arise from any of these compartments. The process and results of lymphocyte transformation in vitro have been studied extensively. B cell lymphomas develop as transformations in the follicular centers of lymphoid tissues. The genesis of T cell lymphomas is less well understood. Both T and B cells have immunoregulatory functions that may be retained by neoplastic lymphoid cells. Many immunological, functional, and cytochemical markers are useful for distinguishing T cells, B cells, and histiocytes; combinations of these markers also distinguish lymphoma/leukemia cells. Cytochemical and histochemical procedures can be used to identify leukemias and lymphomas, although no one stain or enzyme is totally specific for a given neoplastic cell type. Immunohistochemistry and immunocytochemistry have become useful in diagnosis, particularly techniques using antibodies conjugated with enzymes. The application of these methods and concepts to the differentiation of lymphomas and leukemias is discussed. Lymphocytic lymphomas are neoplasms of the immune system that may represent cells that are blocked in certain stages of their normal development or transformation. (22 Refs)

32. ADJUVANT RADIATION THERAPY COMPARED WITH CYCLIC CHEMOTHERAPY IN PATIENTS WITH MAMMARY CARCINOMA. I. CHANGES OF BLOOD LYMPHOCYTE SUBPOPULATIONS.

Petrini B, Wasserman J, Baral E, Blomgren H, Strender LE

Central Microbiological Lab., PO Box 177, S-101 22 Stockhom, Sweden

Acta Radiol Oncol Radiat Phys Biol; 20(2):137-141 1981

Peripheral lymphocyte subpopulations were examined in 37 women with breast carcinoma who were postoperatively randomized to adjuvant local radiation therapy or cyclic treatment with 5-fluorouracil, methotrexate and chlorambucil. Both T and non-T lymphocyte counts were reduced but the latter subpopulation was reduced to the highest relative extent in both groups of patients. Following radiation therapy the non-T cells repopulated more rapidly than the T cells, whereas the repopulation seemed to be the reverse in patients treated with chemotherapy. (Author abstract) (15 Refs)

33. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

Eighteen monographs present experimental and human data for the following antineoplastic and immunosuppressive agents: 5-azacytidine, azathioprine, bischloroethyl nitrosourea, bleomycins (sulfates and hydrochlorides), chlorambucil, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, cisplatin, cyclophosphamide, dacarbazine, 5-fluorouracil, isophosphamide, 6-mercaptopurine, methotrexate, prednisone, procarbazine hydrochloride, treosulfan, vinblastine sulfate, and vincristine sulfate. Section 1 of each monograph summarizes chemical and physical properties; Section 2 describes production, use, occurrence, and analysis. Section 3 covers biological data relevant to evaluation of carcinogenic risk in humans, including carcinogenicity studies, toxic effects, metabolic data, mutagenicity and other short-term tests, and when available case reports or epidemiological studies of cancers present in patients treated with the compound. Section 4 summarizes pertinent animal and human data and gives critical views of the IARC Working Group. (1452 Refs)

34. BLAST-FORMATION OF HUMAN PERIPHERAL LYMPHOCYTES WITH VARIOUS ANTI-LYMPHOCYTE GLOBULINS. REPORT 1. INFLUENCE OF VARIOUS ALGS ON NORMAL HUMAN PERIPHERAL LYMPHOCYTES.

Matsuo E, Saito Y, Shindo K, Matsuo Y, Ikeda M, Kanetake H, Kusaba Y, Hirose T, Kondo A, Morisue S
Dept. Urology, Nagasaki Univ. Sch. Medicine, Nagasaki, Japan
Nippon Hinyokika Gakkai Zasshi; 72(5):573-578 1981

Mitogenic effects of anti-lymphocyte globulins (ALGs; Lots 007, 013, 017, and 020) on human lymphocytes were investigated in vitro on normal human peripheral lymphocytes. Intensive mitogenicity was observed in the ALG against splenic lymphocytes (Lot 007) and in the ALG against peripheral blood lymphocytes (Lot 013), but only slight mitogenicity was observed for the ALGs against human cultured lymphoblasts (Lots 017 and 020). Mitogenic activities were depressed in Lots 013, 017, and 020 in the presence of a complement. Strong lymphoblastic response was observed with Lot 013 at concentrations as low as 0.5 mg/ml when complement was not present, but the effect was slight with high concentrations (5.0 mg/ml). (17 Refs) (In JPN)

35. EVALUATION OF IMMUNOCHEMOTHERAPY FOR ADVANCED CANCER BASED ON THE CELLULAR IMMUNITY.

Sawai K
Third Dept. Internal Medicine, Kyoto Prefectural Univ. Medicine, Kamigyo-ku, Kyoto 602. Japan
Kyoto Furitsu Ika Daigaku Zasshi; 90(4):303-321 1981

Peripheral blood of 241 untreated patients with cancer was examined for blastoid transformation. In the smear method, the av value for healthy adults was 62.9 +-9.7%, while that for the cancer patients was 50.3 +-12.3%. With the microplate method, the values were 92.7 +-35.0 and 28.6 +-23.0, respectively. There were no significant differences among primary cancers of the stomach, liver, colon, lung, kidney, breast, and uterus. The blastoid transformation rate had already decreased in four patients in the early stage of gastric cancer. The group treated by chemotherapy alone showed a decrease in the transformation rate after treatment in 11 out of 21 cases and an increase in 6. In the group treated with only an immunostimulator, the rate increased in eight out of nine cases. This phenomenon, however, was not correlated with a direct tumor effect. Among the cases treated with both immuno- and chemotherapy, the transformation rate was normal or increased in 20 of 36 patients treated with OK-432. In those cases both direct tumor-reducing effect judged by Karnofsky's criteria and longer survival were achieved. Regarding the relationship between the immunological markers and prognosis, the group with a normal transformation rate before treatment showed good prognosis, and extended survival was definite in patients in whome normal values were maintained even after treatment. These results suggest that immunochemotherapy is more effective than chemotherapy alone, especially in patients with high levels of immunological markers before treatment. (63 Refs) (In JPN)

36. IMMUNOLOGICAL STUDIES OF GASTRIC JUICE EXTRACTS FROM GASTRIC CANCER PATIENTS ON MITOGEN INDUCED LYMPHOCYTE TRANSFORMATION.

Ishigami H
First Dept. Surgery, Sch. Medicine, Chiba Univ., Inohana, Chiba 280, Japan
Nippon Geka Gakkai Zasshi; 82(3):230-236 1981

Under tetragastrin stimulation, gastric secretions were collected from 21 gastric cancer patients, 8 peptic ulcer patients and 8 healthy volunteers while keeping intragastric pH at 7. Consistent quantities of proteins were gathered from each of 10 gastric cancer patients, 8 peptic ulcer patients and 8 healthy volunteers, were mixed together by group and the mixtures were then named extract of gastric cancer secretions, extract of peptic ulcer secretions, and extract of healthy volunteer's secretions, respectively. The influence of 100 ug/ml protein of these extracts upon phytohemagglutinin (PHA), concanavalin A (Con A) or Sepharose protein A (SpA)-induced lymphoproliferative response of normal peripheral lymphocytes was evaluated by 3H-thymidine uptake into DNA. When the extract of gastric cancer secretions was first added to the lymphocyte culture with the mitogens listed above, the stimulation index (SI: ratio of cpm with mitogen and extract to cpm without mitogen) was significantly lower than the SIs obtained with the other two extracts. When the extract of gastric cancer secretions was added to culture at 2-hr intervals for 24 hr, the point of suppression of lymphoproliferation was observed to be in the early stage of lymphocyte transformation. Influence of the extract of gastric cancer secretions on mitogen-induced LP was also evaluated on the basis of the size of the tumors from which the secretions were obtained; suppressive activity was observed mainly in the extract from tumors 10-20 square cm. The results suggested that the extract of gastric cancer secretions, chiefly from tumor size 10-20 square cm, possesses suppressive activity on both T and B cells, and the point of suppression is in the early stage of lymphocyte transformation. (18 Refs) (In JPN)

37. USE OF LEVAMISOLE, AN IMMUNE CONTROLLING AGENT IN VARIOUS CLINICAL CONDITIONS MAINLY LIVER DISEASES.

Miyake M
No 2-2-5-Chome, Higashinmechi, Omuta, Fukuoka 836, Japan
Fukuoka Igaku Zasshi; 72(6):368-378 1981

Results of levamisole (LM) treatment in patients with diseases associated with decreases in T-cell counts are reported. LM induced an increase in T cells and played a major role in suppressing recurrences in patients with acute aggressive hepatitis, chronic hepatitis, and liver cirrhosis. Its effectiveness was confirmed in a long-term comparison with other drugs. Abnormally elevated values in liver function tests tended to return to normal, along with general improvement, in the LM group. No such changes occurred in the control groups. Excellent results were also obtained in patients with hepatoma, gastric carcinoma, rheumatoid arthritis, herpes zoster, and influenza. (30 Refs) (In JPN)

38. IN VIVO AUGMENTATION OF NATURAL KILLER (NK) ACTIVITY BY A STREPTOCOCCAL PREPARATION OK-432: CHARACTERIZATION OF EFFECTOR CELLS AND INDUCTION OF INTERFERON IN SERA.

Wakasugi H, Miyata M, Morioka Y, Oshimi K, Kasahara T, Takahashi K, Saito M, Ebina T
Dept. Surgery, Jichi Medical Sch., Japan
Nippon Gan Chiryo Gakkai Shi; 16(3):433-446 1981

The effects of pre- and/or postoperative treatment with streptococcal preparation OK-432 on natural killer (NK) cell activity and interferon titers were studied in 40 patients with stomach, breast, pancreas, or colon cancer. The patients received a first OK-432 course beginning on postoperative days 7-35 (Group I) or a second course beginning on postoperative days 8-52 (Group II), 6-20 (Group III), or 5-43 (Group IV). Patients in Groups I, II, and III showed significantly augmented killer cell activity within 3 days of initial OK-432 inoculation. Characterization of effector cells from Group IV patients showed that they were NK cells (T and non-T cells and IgG-Fc receptor-positive cells). Induced IF titers studied in Groups I, II, and III did not correlate with levels of augmented NK activity. Four Group III subgroups were distinguished according to degree of NK activity and IF titers: patients with low IF titers that declined with augmented NK activity, patients with low titers that increased with augmented NK activity, patients in whom IF was detected continuously without NK augmentation, and patients with augmented NK activity but no significant IF induction. (40 Refs) (In JPN)

39. THE EFFECT OF BESTATIN ON THE LYMPHOCYTE FUNCTIONS OF CANCER PATIENTS.

Noma T, Yata J, Hoshi K, Ishii T
Dept. Pediatrics, Tokyo Medical and Dental Univ., Tokyo, Japan
Nippon Gan Chiryo Gakkai Shi; 16(3):453-459 1981

Bestatin was administered to 31 patients with digestive tract cancer before any other therapeutic treatment. The drug enhanced the helper function of T cells in immunoglobulin (Ig) production in approx one-half of the patients, and it activated mitomycin C-sensitive T cells that suppressed Ig production in most patients. In approx one-third of the patients, bestatin also augmented the natural killer and cytotoxicity activity of T cells against allogeneic target cells. (23 Refs) (In JPN)

40. INFLUENCES OF AN EXTRACT FROM TUBERCLE BACILLI OF HUMAN TYPE (SSM) ON THE FUNCTION OF HUMAN LYMPHOCYTES: EFFECTS ON POKEWEED MITOGEN-INDUCED IMMUNOGLOBULIN PRODUCTION BY HUMAN LYMPHOCYTES.

Yamakura T, Takahashi K, Shimbo T, Ohtsuka Y
Lab. Immunology, Toho Univ., Japan
Nippon Gan Chiryo Gakkai Shi; 16(3):447-452 1981

SSM human tubercle bacilli extract did not augment in vitro immunoglobulin biosynthesis in normal human lymphocytes in the presence of pokeweed mitogen. However, SSM reversed the depression of lymphocyte function caused by treatment with sera from gastric cancer patients; it also inhibited cancer sera-induced lymphocyte depression. These results were also seen in lymphocytes from healthy subjects with negative purified protein derivative skin tests. (17 Refs) (In JPN)

41. COWDEN'S DISEASE ASSOCIATED WITH IMMUNODEFICIENCY.

Ruschak PJ, Kauh YC, Luscombe HA
Dept. Dermatology, Thomas Jefferson Univ., Jefferson Medical Coll., Philadelphia, PA
Arch Dermatol; 117(9):573-575 1981

Cowden's disease is an autosomal dominant disease characterized by verrucous lesions, mucosal papules, and trichilemmomas associated with gastrointestinal tract, thyroid, CNS, and musculoskeletal abnormalities. In addition, our patient exhibited a deficiency of T-lymphocyte function, with recurrent cellulitis and abscess formation, and the eventual development of acute myelogenous leukemia. The defect in T-lymphocyte function may help to explain the higher incidence of malignant neoplasms in patients with Cowden's disease. We recommend complete immunologic examination of patients with this disorder. (Author abstract) (15 Refs)

42. CHROMOSOME STUDIES IN ADULT T-CELL LEUKEMIA IN JAPAN: SIGNIFICANCE OF TRISOMY 7.

Ueshima Y, Fukuhara S, Hattori T, Uchiyama T, Takatsuki K, Uchino H
Dept. Medicine, Box 420, Univ. Chicago, Chicago, IL, 60637
Blood; 58(3):420-425 1981

Chromosomes were studied in cells from 15 Japanese patients with adult T-cell leukemia (ATL). Mitoses were obtained from unstimulated peripheral blood in 12 patients and a lymph node in 1 patient. In two other patients, mitotic cells were obtained solely from peripheral blood stimulated with phytohemagglutinin (PHA). Chromosomally abnormal cells were seen in 14 of the 15 patients. The abnormal cells had a modal number of chromosomes in near diploid range in 12 patients, and in near triploid and tetraploid range in the remaining 2 patients, respectively. Eight of the nine patients analyzed by Q-banding had clonal chromosome abnormalities. The most common abnormality was trisomy number 7 or 7q, which was seen in five cases and has been primarily observed in lymphoid neoplasms. A 14q+ marker chromosome was found in two patients and a Dq+ in one patient; loss of a sex chromosome was found in three patients. Most chromosomes were involved in gains, losses, or structural rearrangements, but abnormalities of number 11, which have been frequently found in lymphoid malignancies, was not observed in our series. The significance of these chromosome abnormalities is discussed. (Author abstract) (37 Refs)

43. CHEMOTHERAPY OF ADVANCED OVARIAN EPITHELIAL CARCINOMA WITH MELPHALAN AND LEVAMISOLE: A PILOT STUDY OF THE GYNECOLOGIC ONCOLOGY GROUP.

Gusdon JP, Homesley HD, Muss HB, Heise ER, Herbst GA, Richards F, Spurr CL, Lovelace JV, Di Saia PJ
Dept. Obstetrics and Gynecology, Bowman Gray Sch. Medicine, 300 S. Hawthorne Road, Winston-Salem, NC, 27103
Am J Obstet Gynecol; 141(1):65-70 1981

Twenty-three patients with Stage III, Stage IV, or recurrent epithelial ovarian cancer were treated with a combination of melphalan and levamisole to determine a tolerable dosage schedule, possible adverse effects, and a general estimate of response rate and duration. In seven patients with measurable disease there were four complete responses (57%) with a median duration of 75 wk. Two of the complete responders have had negative second-look laparotomies while the other two patients have had subsequent progression. Of 16 patients with nonmeasurable disease, 2 have had negative second-look laparotomies and 2 remain progression free. Thus 8 of 23 patients (35%) had complete responses or remain progression free whereas 4 of 23 patients (17%) have had negative second-look laparotomies. No serious toxicity was encountered. Immunologic monitoring did not indicate significant immunologic reconstitution in these immunosuppressed patients. (Author abstract) (22 Refs)

44. T GAMMA CELLS: A MISSING LINK BETWEEN MALIGNANT HISTIOCYTOSIS AND T CELL LEUKEMIA-LYMPHOMA?

Kadin ME
Dept. Lab. Medicine and Pathology, SB-10, Univ. Washington Sch. Medicine, Seattle, WA, 98105
Hum Pathol; 12(9):771-772 1981

Attempt was made to explain the rapid development of malignant histiocytosis (MH) or histiocytic medullary reticulosis-like syndrome in the patients with acute lymphocytic leukemia and T cell lymphoma. The short interval between the start of therapy for leukemia and onset of the second disorder excluded the drug-induced etiology of histiocytosis. The chance coincidence of two diseases was also highly unlikely. Histologic and immunologic examination of the patients with MH accompanying acute leukemia showed an increasing number of histiocytes. The tumor cells had receptors for both unsensitized sheep RBC and IgG coated ox or sheep RBC indicating the lymphocyte subpopulation known as T gamma cells. (15 Refs)

45. MECHANISMS OF ANTI-TUMOR ACTION OF CORYNEBACTERIUM PARVUM. I. POTENTIATED TUMOR-SPECIFIC IMMUNITY AND ITS THERAPEUTIC LIMITATIONS.

Dye ES, North RJ, Mills CD
Trudeau Inst., Inc., Saranac Lake, NY, 12983
J Exp Med; 154(3):609-620 1981

A model currently being used to analyze the potential and limitations of tumor immunotherapy with Corynebacterium parvum is described. It was shown that implanting of the hind footpad of mice with 2 x 10(6) P815 mouse mastocytoma or methylcholanthrene (Meth A)-induced tumor (Meth A fibrosarcoma) cells admixed with 100 ug C parvum resulted in the emergence of a tumor that grew for a period of 9-10 days and then regressed. Regression of the C parvum-treated tumor failed to occur in mice that were gamma-irradiated, or made T cell deficient by thymectomy and lethal irradiation, and restored with bone marrow cells. These results, together with the finding that the onset of C parvum-induced tumor regression was associated with the generation in the spleen and draining node of T cells that were capable of adoptively immunizing normal mice against growth of a tumor implant, was consistent with the hypothesis that the therapeutic effect of C parvum is based on its capacity to potentiate the generation of T cell-mediated antitumor immunity. It was also shown that the mechanism responsible for this regression was capable of causing the regression of an untreated test tumor growing at a distant site, and that this therapeutic action was based on a T cell-mediated immune response to tumor-specific transplantation antigens. The immunotherapeutic action of the C parvum-tumor cell admixtures against a distant test tumor was limited to a test tumor below a certain critical size. (23 Refs)

46. IMMUNOSTIMULATION IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Konopka L, Ciesluk S, Zywicka-Lopaciuk H, Maslanka K, Sylwestrowicz T, Pawelski S, Karpowicz M
Instytut Hematologii, Chocimska 5, Warsaw, Poland
Przegl Lek; 38(5):437-441 1981

The effect of immunostimulation with levamisole (450 mg/wk for 6 wk or 150 mg/wk for 12 wk) on humoral and cellular immunity was studied in 25 patients with chronic lymphocytic leukemia. The patients were not receiving cytostatic and hormone treatment immunity (reduction of the IgA and IgM levels) was observed before levamisole treatment in all 25 patients. Improvement of the initially negative delayed hypersensitivity test was observed after levamisole treatment in 50% of the patients, and the DNA synthesis in lymphocytes was noted in 32%. The results confirm the beneficial immunoregulatory effect of levamisole in all patients. (15 Refs) (In POL)

47. MORPHOLOGICAL AND CYTOCHEMICAL CHARACTERISTICS OF PERIPHERAL BLOOD MONOCYTES AND NEUTROPHILS IN CHILDREN WITH ADVANCED VARIANTS OF HISTIOCYTOSIS X.

Skorobogatova OV, Finogenova NA
Dept. Pediatrics, N. I. Pirogov Second Medical Inst., Moscow, USSR
Pediatriia; (8):32-36 1981

The functional state of the peripheral blood neutrophils and monocytes was studied in 38 children (25 boys, 13 girls; aged 2 mo to 15 yr) with histiocytosis X (HX). The changes recorded in the neutrophils were similar to those in children with bacterial infections. The changes in the circulating monocytes included predominance of immature cells, high level of peroxidase, decreased level of acid phosphatase and alpha-naphthylesterase, and increased level of glycogen. Functional insufficiency of monocytes was retained during the remission. Treatment with levamisole was found to normalize the functional activity of monocytes and to improve the general state of HX patients. (5 Refs) (In RUS)

48. PHAGOCYTIC ACTIVITY OF NEUTROPHIL LEUKOCYTES AND MONOCYTES DURING THE REMISSION OF ACUTE LEUKEMIA AFTER CHEMOTHERAPY AND IMMUNOTHERAPY WITH BCG VACCINE AND LEVAMISOLE.

Dosimov ZhB, Skorobogatova OV, Rumiantsev AG, Eremeev VS

Dept. Pediatrics, N. I. Pirogov Second Medical Inst., Moscow, USSR

Pediatriia; (8):26-28 1981

Phagocytic activity (PA) of neutrophils and monocytes was studied in 42 children (aged 3 to 14 yr) with acute lymphoid leukemia. All patients were in complete remission of 6-36-mo duration; the patients received continuous maintenance chemotherapy and/or immunotherapy with BCG vaccine and levamisole. There was a marked inhibition of PA of neutrophils and monocytes in the patients undergoing chemotherapy. PA of monocytes in children undergoing immunotherapy with BCG vaccine was comparable to that in healthy controls. (20 Refs) (In RUS)

49. LYMPHOCYTES INFILTRATING HUMAN BREAST CANCERS LACK K-CELL ACTIVITY AND SHOW LOW LEVELS OF NK-CELL ACTIVITY.

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Br J Cancer; 44(2):166-176 1981

Lymphocytes infiltrating human primary mammary carcinomas lack ADCC and show low levels of natural cytotoxicity. The peripheral blood lymphocytes, however, show a variable but prominent level of cytotoxicity. Lymphocyte preparations from breast tumors, when mixed with autologous blood lymphocytes, significantly suppress their prominent killer- (K- and NK-) cell activities. (Author abstract) (34 Refs)

50. PRETREATMENT TESTICULAR BIOPSY IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKAEMIA.

Kim TH, Brynes RK, Lui VK, Hargreaves HK, Hawkins HK, Woodard J, Ragab AH

Dept. Pediatrics, Emory Univ. Clinic, 1365 Clifon Road, Atlanta, GA, 30322

Lancet; 2(8248):657-658 1981

Between August, 1978, and March, 1981, 24 boys with acute lymphocytic leukemia (ALL) (14 non-B-cell non-T-cell, 6 pre-B-cell, and 4 T-cell) underwent bilateral wedge testicular biopsy at initial diagnosis. All testes were of normal size. Histological analysis was performed independently by three pathologists, 4 (3 non-B non-T, and 1 pre-B) of 20 patients with non-T-cell ALL demonstrated testicular focal lymphoblastic involvement. Successful induction chemotherapy without concomitant testicular irradiation completely eradicated testicular infiltrates in all four patients. Only one of the four T-cell patients had pre-treatment testicular infiltrates. Unlike boys with non-B non-T leukemia, attainment of bone-marrow remission in this patient was associated with persistent testicular disease. These preliminary data indicate that in patients with ALL of non-T cell type, systemic induction chemotherapy eradicates the small testicular infiltrates of lymphoblasts. Prophylactic testicular irradiation in this group of patients does not seem to be warranted. (Author abstract) (10 Refs)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

51. ANTITUMOR ACTIVITY OF LACTOBACILLUS CASEI IN MICE.

Kato I, Kobayashi S, Yokokura T, Mutai M
Yakult Central Inst. Microbiological Res., 1796 Yaho, Kunitachi-shi, Tokyo 186, Japan
Gan; 72(4):517-523 1981

The effect of Lactobacillus casei YIT 9018 (LC 9018) on the growth of transplantable allogeneic and syngeneic mouse tumors was studied. Ip treatment of LC 9018 caused a significant prolongation of the life span of ICR mice inoculated with sarcoma-180 ip and BDF1 mice inoculated with L1210 leukemia ip. Iv injection of LC 9018 markedly inhibited the growth of sc inoculated sarcoma-180. This organism was also effective against methylcholanthrene-induced syngeneic MCA K-1 tumor in BALB/c mice. The antitumor activity of LC 9018 was reduced by treatment with carrageenan, an anti-macrophage agent, and was also observed in T-cell deficient athymic nude mice. These results suggested that the antitumor activity of LC 9018 may be macrophage-dependent. (Author abstract) (20 Refs)

52. IMMUNOLOGICAL STUDIES ON THE ANTITUMOR EFFECT OF SPORAMYCIN.

Umezawa I, Komiyama K, Kawakubo Y, Koyanagi N, Arai H, Nishiyama Y
Kitasato Inst., 9-1, Shirokane 5-chome, Minato-ku, Tokyo 108, Japan
Gan; 72(4):598-603 1981

The role of immunological effects in the antitumor activity of sporamycin was studied mainly using the mouse syngeneic tumor, Meth-A. Sporamycin inhibited the growth of the Meth-A tumor in BALB/c mice, and 12 out of 19 mice were cured. The 12 survivors did not show any growth of reinoculated Meth-A cells. Enzyme-histochemical observations revealed marked activities of both acid phosphatase and alpha-naphthyl acetate esterase in lymphoid cells and macrophages which heavily infiltrated the tumor tissue. Pretreatment of mice with sporamycin produced a remarkable inhibition of tumor growth. A marked neutralization activity against tumor cells was observed by Winn's method using spleen cells of tumor-bearing mice which had been pre- or post-treated with sporamycin. However, this neutralization activity was depressed by anti-Thy 1.2 serum plus complement. The response of spleen cells to concanavalin A was increased by treatment with sporamycin in mice. All of these findings suggest that sporamycin may, at least partially, act by modulating the cellular immune response. (Author abstract) (7 Refs)

53. INCREASE OF T CELLS IN THE LIVER DURING HEPATOCARCINOGENESIS WITH N-2-FLUORENYLACETAMIDE IN RATS.

Okita K, Ando K, Fukumoto Y, Miyazaki M, Tsubota W, Kodama T, Takemoto T
Dept. Internal Medicine, Yamaguchi Univ. Sch. Medicine, 1144 Kogushi, Ube 755, Japan
Gan; 72(4):610-614 1981

The localization of thymus-derived lymphocytes (T cells) was investigated in rat liver by the immunofluorescence method during hepatocarcinogenesis with N-2-fluorenylacetamide. In the early stage of carcinogenesis, the number of T cells never increased significantly in livers in which hyperplastic liver nodules (population I) were seen. On the other hand, in the late stage of carcinogenesis, T cells extensively invaded hyperplastic nodules (population II) as well as hepatomas. According to the concept of cell-mediated immunity, hyperplastic nodules in the late stage might have a neoantigen(s) which evokes the response of T cells. Therefore, it may be concluded that populations I and II are biologically distinct lesions in spite of their histological identity. (Author abstract) (13 Refs)

54. HUMAN MELANOMA GROWTH IN THE PERITONEAL CAVITY OF THE ATHYMIC MOUSE - A MODEL FOR IN VIVO STUDY OF CELL-MEDIATED IMMUNITY.

Akimaru K, Stuhlmiller GM, Seigler HF
(c/o Seigler), Duke Univ. Medical Center, Durham, NC, 27710
J Surg Oncol; 17(4):309-320 1981

Ip injections of 2 x 10(7) SH-Me cells (human metastatic melanoma cells) to 20 BALB/c nu/nu mice (Group A) and 1 x 10(7) cells to 20 mice (Group B) were performed. All animals were studied clinicopathologically. Five animals in Group A were sacrificed serially, revealing marked tumor growth of the melanoma within the peritoneal cavity. These tumors grew in multiple nodular configurations and tumor ascites was present by the 3rd wk. The remaining 15 animals in Group A were allowed to progress and 7 subsequently died with mouse viral hepatitis (MVH). These animals had suppressed tumor growth. The remaining eight animals died of peritoneal carcinomatosis with survival time of 24.1 +-5.0 days. Eight of the animals in Group B died of mouse viral hepatitis while the remainder died of peritoneal tumor without distant metastasis. Survival time in these animals was 23.8 +-2.6 days. Both 2 x 10(7) and 1 x 10(7) tumor cells injected ip will constantly produce tumor nodules in non-MHV-infected nude mice with similar survival. This experimental model has proven useful for in vivo study to assess the immunoreactivity of melanoma patient cells reactive against target tumor cells. (Author abstract) (14 Refs)

55. ESCAPE OF METASTASIZING CLONAL TUMOR CELL VARIANTS FROM TUMOR-SPECIFIC CYTOLYTIC T LYMPHOCYTES.

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J Exp Med; 154(2):557-562 1981

The spontaneous, highly metastatic ESb tumor variant arose from the chemically-induced DBA/2 lymphoma L5178Y (Eb) tumor. It is characterized by a tumor-associated transplantation antigen (TATA). This antigen is recognized by syngeneic secondary antitumor cytolytic T lymphocytes (CTL). During metastasis of twice-cloned cell lines of this tumor, immunoresistant variants develop that are not susceptible to lysis by CTL. These variants are detected in the spleens of normal syngeneic mice. Experimental evidence indicates that ESb TATA is reduced or non-existent in the variants. They apparently did not have a differentiated TATA. The variants remained stable in over 100 tissue culture generations. They were shown not to be preexisting in the original tumor cell population. The high frequency with which these variants occur is suggested as a cause of the ineffectiveness of specific immunization against the ESb tumor type. (15 Refs)

56. REJECTION OF ALLOGENEIC TUMOR CELLS GROWING IN MOUSE CEREBROSPINAL FLUID: FUNCTIONAL ANALYSIS OF THE INFLAMMATORY PROCESS.

Doherty PC, Zinkernagel RM, Ramshaw IA, Grant CK
Wistar Inst., 30th and Spruce St., Philadelphia, PA, 19104
J Neuroimmunol; 1(1):93-99 1981

In C57BL/6 mice (H-2b) inoculated intracerebrally with P815 mastocytoma (H-2d), the tumor cells multiplied rapidly in the cerebrospinal fluid (CSF) for 5 days, then were completely eliminated from the CSF in the next 3 days. On day 8, the CSF contained large numbers of inflammatory cells, which were identified as potent cytotoxic T-lymphocytes, as well as phagocytic and nonphagocytic cells capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) against 51Cr-labeled P815 cells. The cytotoxicity of the CSF cells presumably reflected the activities of K cells and cells of the monocyte-macrophage series. The levels of antibody capable of sensitizing the tumor cells to both ADCC and complement-mediated lysis were about 1,000x higher in the serum than in the CSF on day 9. Spleen cells, obtained on day 8, were much less active in the ADCC test than the CSF inflammatory cells obtained at the same time. Sensitive complement-dependent and lymphocyte-dependent cytotoxic assay systems demonstrated no tumor-specific antibody in the CSF of mice that had recently rejected the allogeneic tumor. The process of cell-mediated tumor rejection did not obviously compromise the blood-CSF barrier to immunoglobulins. (18 Refs)

57. NATURAL KILLING BY SPLEEN CELLS FROM W/WV AND SL/SLD ANEMIC MICE.

Seaman WE, Talal N
Veterans Admin. Medical Center (151T), 4150 Clement St., San Francisco, CA, 94121
Exp Hematol; 9(7):691-696 1981

Natural killer cells are mononuclear cells that spontaneously lyse certain tumor cell lines without prior sensitization to the target. In mice, precursors of natural killer cells exist in the bone marrow. Moreover, natural killing is thought to be 'marrow-dependent' because irradiation of the marrow in vivo with 89strontium reduces natural killing outside the marrow. We examined natural killing in W/Wv mice, which are congenitally anemic because of a defect in erythropoietic stem cells, and in congenitally anemic Sl/Sld mice, which have a defect in the host environment that prevents effective erythropoiesis. Young (6-8 wk) W/Wv mice had reduced levels of natural killing when compared to their normal littermates. The defect in W/Wv mice is discussed in relation to their defects in erythropoiesis. Sl/Sld mice had normal levels of natural killing, demonstrating that the defect in erythropoietic environment does not affect the generation of NK cells. (Author abstract) (33 Refs)

58. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.

Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981

Literature data on tumor factors that can stimulate or inhibit proliferation of normal or neoplastic cells are reviewed. Factors isolated from murine sarcoma 180, spontaneous and explanted murine mammary gland carcinomas, tissue-specific inhibitors of cell divisions (chalones), and polysomal RNA from

Rous sarcoma cells were found to regulate the neoplastic growth and to affect tumor transplantability. Tumor factors were shown to inhibit the antibody formation. The sera of cancer patients was shown to contain factors that inhibited lymphocyte cytotoxicity. In response to stimulation with tumor antigens, T lymphocytes formed the clone of killer cells. The degree of lymphocyte transformation depended upon the ratio of lymphocytes and tumor antigen. Tumor factors were found to inhibit not only the antitumor but also the transplacental immunity. Stimulation of tumor antigenicity can stimulate the immune system of tumor-bearing organism and thus can have an immunotherapeutic effect. (108 Refs) (In RUS)

59. EFFECT OF NOCARDIA RUBRA CELL-WALL SKELETON TREATMENT ON TUMOR FORMATION IN TWO-STAGE CHEMICAL CARCINOGENESIS OF MOUSE SKIN.

Inoue T, Yoshimoto T, Ogura T, Hirao F, Azuma I, Yamamura Y
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Cancer Immunol Immunother; 11(3):207-210 1981

Male C57BL/6 mice were painted at age 11 wk on the dorsal skin with 20 ug 7,12-dimethylbenz[a]anthracene (DMBA). Beginning 7 wk later they were painted with 2.5 ug 12-O-tetradecanoyl-phorbol-13-acetate (TPA) 2x/wk for 30 wk. Three groups of mice were treated with sc injections of 100 ug Nocardia rubra cell-wall skeleton (N-CWS) 1x/wk for 7 wk. Group 1 received the N-CWS before initiation with DMBA. Group 2 received N-CWS between initiation and promotion with TPA. Group 3 received N-CWS beginning at the start of promotion. A fourth group recieved no N-CWS treatment. All N-CWS-treated groups showed prolongation of the latent period before appearance of the first tumor. Group 1 exhibited the most significant reduction in incidence of skin tumor (5/17 30 wk from the beginning of promotion vs 13/19 in Group 4) and number of tumors/survivor (0.35 at 30 wk vs 1.74 in Group 4). N-CWS was effective in group 3 until 20 wk after the beginning of promotion. It was also effective in group 2 at 15 wk after the beginning of promotion, but overall tumor yield was the same in groups 2 and 4. N-CWS may inhibit carcinogenesis by enhancing immunological surveillance at the promotion stage or by activating macrophages which sequester DMBA. (24 Refs)

60. MORPHOLOGICAL AND FUNCTIONAL ASPECTS OF ACTIVE SPECIFIC IMMUNOTHERAPY OF ESTABLISHED PULMONARY METASTASES IN GUINEA PIGS.

Hanna MG, Peters LC
Cancer Metastasis and Treatment Lab., NCI Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 41(10):4001-4009 1981

Using active specific immunotherapy, we evaluated the efficacy of syngeneic tumor cell vaccines supplemented with the adjuvant Mycobacterium bovis strain BCG against established pulmonary metastases. In a series of experiments, inbred strain 2 guinea pigs were given iv injections of 10(6) syngeneic hepatocarcinoma cells (100x the minimum lethal dose). Animals were not treated or were treated once a wk for 2 wk with vaccines consisting of 10(7) cryopreserved, x-irradiated viable tumor cells admixed with 10(7) live BCG and on the 3rd wk with a vaccine consisting of 10(7) tumor cells alone. To assess the limits of tumor burden in this model, we immunized groups of animals on days 1, 4, 7, or 10 after iv tumor challenge. The pulmonary tumor foci ranged from clumps of several cell at day 1 to nodules between 0.1 and 0.2 mm in diameter at day 10. By days 21 to 24 after iv tumor challenge, the pulmonary nodules were macroscopic in size, equal to or greater than 0.5 mm in diameter. While significant protection was measured by survival, the effectiveness of this combination of tumor cells plus BCG was limited by tumor burden. Morphological evaluation of pulmonary tumor foci in treated animals revealed mononuclear cell infiltration characteristic of a cell-mediated hypersensitivity reaction in the time interval between the first and second immunization. By the time of the third immunization, the nodules had progressed to a marked histiocytosis with fibrosis and central necrosis. It is possible not only that these specific immunological reactions accomplish a significant reduction of the tumor mass but that the host-mononuclear cell infiltrate disrupts the organized histological architecture of metastatic clones, perhaps by the release of soluble factors such as lymphokines. This disruption of the organized histological architecture of the metastatic clones creates a state in which the tumor cells may be more vulnerable or exposed, by destroying the anatomic barriers that allow the tumor to escape disruption by a variety of antitumor agents. This report suggests that multimodality therapy such as postsurgical active specific immunotherapy would be enhanced in combination with other antitumor agents, which on their own would be limited by the anatomical organization of micrometastatic nodules. (Author abstract) (48 Refs)

61. SUPPRESSOR PATHWAYS IN TUMOR IMMUNITY: A REQUIREMENT FOR QA-1 POSITIVE TUMOR-BEARER SPLEEN T CELLS IN SUPPRESSION OF THE AFFERENT IMMUNE RESPONSE TO TUMOR ANTIGENS.

Mule JJ, Stanton TH, Hellstrom I, Hellstrom KE
Div. Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Int J Cancer; 28(3):353-359 1981

Spleen cells from mice bearing large methylcholanthrene (MCA)-induced sarcomas were injected iv into mice challenged in the hind footpads with heavily-irradiated cells from the same or a different sarcoma. As measured by [3H]-thymidine incorporation on day 5 or 6, cellular proliferation in the draining popliteal lymph nodes of these mice was significantly depressed as compared to control animals receiving normal spleen cells or medium iv. The suppression was found to be mediated by a Qa-1-positive, Thy-1-positive cell. It was relatively resistant to cyclophosphamide treatment (100 mg/kg). Furthermore, it had both antigen-specific and non-specific components. The findings are discussed in relation to a suppressor activator cell-suppressor acceptor cell pathway in the immunoregulation of tumor immunity. (Author abstract) (38 Refs)

62. AN EXPERIMENTAL STUDY OF PASSIVE CANCER IMMUNOTHERAPY BY INFUSION OF IMMUNE LYMPHOCYTES.

Mochizuki T
First Dept. Surgery, Juntendo Univ., Sch. Medicine, Bunkyo-ku, Tokyo 113, Japan
Nippon Geka Gakkai Zasshi; 82(3):193-202 1981

Experiments were first carried out to see whether cryoimmunity for cancer is induced. The tumors of rats were treated by freezing, and their peripheral lymphocytes were collected and infused into other rats. We observed by the challenge of the same tumor cells and macrophage migration inhibition test whether antitumor activity was transferred to these rats. The rats receiving the infusion rejected the tumor challenge at a high frequency. The lymphocytes collected from these rats specifically inhibited the migration of macrophages. From these results, the establishment of cryoimmunity in the primary rats was proved. Further experiments were carried out to evaluate the effects of the same lymphocytes infused into the tumor-bearing rats. Remarkable inhibition of tumor growth and elongation of mean survival days were observed. These effects depend on the dose of infused lymphocytes. Remarkable infiltration of lymphocytes in the tumor tissue after infusion was seen by means of histological study. (28 Refs) (In JPN)

63. CHANGES IN THE PERITONEAL MACROPHAGE CYTOSTATIC ACTIVITY CAUSED BY THE ADMINISTRATION OF IMMUNOPOTENTIATORS AND ANTICANCER AGENTS IN NORMAL AND TUMOR-BEARING RATS.

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Second Dept. Surgery, Tokyo Medical and Dental Univ., Bunkyo-ku, Tokyo 113, Japan
Ochanomizu Igaku Zasshi; 29(1):11-22 1981

The peritoneal macrophage cytostatic activity (PMCA) of normal and Sato lung cancer (SLC)-bearing Donryu rats that had been given Nocardia rubra-cell wall skeleton (N-CWS) or BCG as an immunopotentiator and 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2 chloroethyl)-3-nitrosourea hydrochloride or cyclophosphamide as an anticancer agent was measured and examined for its correlation with antitumor activity. When immunopotentiators were given to normal rats, the effect on the PMCA varied with the type of immunopotentiator and the route, method and period of administration. The increase in in vitro cytostatic activity correlated well with the results obtained by in vivo Winn-type neutralizing tests. The PMCA of the tumor-bearing rats was lower than that of the control rats, but was restored or even improved by the administration of immunopotentiators. When anticancer drugs were given to normal rats, the decrease in macrophage function was prevented by the simultaneous administration of immunopotentiators. The tumor growth-inhibiting effect of immunochemotherapy in tumor-bearing rats was stronger than that of immunotherapy or chemotherapy given alone. On the other hand, PMCA was also markedly increased in the rats given immunochemotherapy, which suggests that potentiated macrophages play a role in the antitumor effect of immunochemotherapy. (42 Refs) (In JPN)

64. ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY IN X-IRRADIATION-INDUCED ADENOCARCINOMA OF THE RAT SMALL BOWEL.

Stevens RH, Cole DA
Radiation Res. Lab., 14 Medical Lab., Dept. Radiology, Univ. Iowa, Iowa City, IA, 52242
Radiat Res; 87(3):635-645 1981

The production of immunoglobulins during antibody-dependent cell-mediated cytotoxicity (ADCC) was studied in x-ray-induced adenocarcinomas in male outbred Holtzman rats. Approx 10-25% of the Holtzman rats, which had only their hypoxic small intestine exposed to the ionizing radiation developed small bowel adenocarcinomas that could be visibly detected, while of the remaining animals (75-90%), few (1-2%) developed identifiable lesions throughout their lifetimes. Positive ADCC was observed for both groups when peripheral blood lymphoid cells (PBLC) from unirradiated control animals were used as the effector cells. For the expression of the ADCC, both the serum-exposed rats and effector cells were found to be necessary for cytotoxicity. No apparent correlation was observed between the existence of visible cancer and the size of the lesion with the level of ADCC. The specificity of the ADCC responses was studied. Cytotoxicity was found to exist in the serum component. Among the majority of animals (75-90%) which had been exposed under identical conditions to the tumorigenic levels of x-rays but failed to develop the visible lesions, circulating immunoglobulins capable of inducing ADCC were found to be present. The serum immunoglobulins responsible for the antitumor immunity were of the IgG class. (39 Refs)

65. MECHANISMS OF ANTI-TUMOR ACTION OF CORYNEBACTERIUM PARVUM. II. POTENTIATED CYTOLYTIC T CELL RESPONSE AND ITS TUMOR-INDUCED SUPPRESSION.

Mills CD, North RJ, Dye ES
Trudeau Inst., Inc., Saranac Lake, NY, 12983
J Exp Med; 154(3):621-630 1981

The capacity of an admixture of Corynebacterium parvum and P815 mastocytoma tumor cells implanted into B6D2 F1 mice to cause the rejection of a small test tumor growing at a distant site was studied in relation to the augmented production of cytolytic T cells in the lymph node draining the site of injection of the therapeutic admixture. A companion paper showed that implanting P815 tumor cells admixed with C parvum resulted in the emergence of a tumor that grew progressively for 9-10 days and then regressed. In addition, it was shown that the onset of tumor regression was preceded by a substantial generation in the draining lymph node and spleen of T cells capable of specifically lysing P815 target cells in vitro. Because the production of cytolytic T cells was much greater in response to the tumor growing in the presence of C parvum than in response to a tumor growing alone, it was suggested that the therapeutic action of C parvum when admixed with the tumor cells is based on its capacity to potentiate the production of cytolytic T cells. The adjuvant action was revealed by the additional finding that gamma-irradiated tumor cells failed to evoke the generation of T cells unless they were injected admixed with C parvum. Additional related study in DBA/2 mice showed generation of less peak cytolytic activity than B6D2 mice in response to C parvum and P815 cells; the tumors in DBA/2 mice did not completely regress. (13 Refs)

66. INTERRELATIONSHIP BETWEEN MONOCYTE MATURATION IN VITRO AND TUMOR GROWTH IN MURINE TUMOR HOST.

Krishnan EC, Krishnan L, Jewell WR
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J Surg Res; 31(3):240-245 1981

A mononuclear cell-rich fraction was isolated from the peripheral blood of normal Sprague-Dawley rats and rats with growing Walker 256 carcinosarcoma. The mononuclear cells were cultured in microtest plates over a period of 7 days. Monocyte maturation was studied, and macrophage precursors were counted periodically as the tumor grew. The number of macrophage precursors diminished as the tumor size became larger. But, when the tumor was excised, the number of macrophage precursors returned to a normal value postoperatively. However, the peripheral blood monocyte counts were not depressed at any time. This observation indicates a monocyte maturation defect in the tumor host. (Author abstract) (20 Refs)

67. PRODUCTION OF INFECTIOUS EPSTEIN-BARR VIRUS IN MOUSE LYMPHOCYTES.

Volsky DJ, Klein G, Volsky B, Shapiro IM
Dept. Pathology, Univ. Nebraska Medical Center, Omaha, NE, 68105
Nature; 293(5831):399-401 1981

Epstein-Barr virus (EBV) DNA replication and antigen expression were studied in CBA or A/Sn mouse lymphocytes rendered EBV-susceptible by virus receptor implantation. EBV-determined nuclear antigen (EBNA) and early and virus capsid antigens were demonstrated in receptor-implanted cells exposed to EBV strains P3HR-1 or B95-8. Although EBNA levels were low, viral DNA replication occurred in 0.3%-4.7% of the infected cells. Unlike human lymphocytes, the mouse lymphocytes could be infected by both EBV strains, and the infectibility was not limited to B lymphocytes. Moreover, infection was not followed by the outgrowth of permanently transformed lymphoid cells and suppression of the virus lytic cycle. Lytically infected mouse cells continued to release infectious virus that induced EBV antigens in target Raji and Lukes cells. (12 R efs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

68. TRANSFER FACTOR IN THE TREATMENT OF HERPES SIMPLEX TYPES 1 AND 2.

Khan A, Hansen B, Hill NO, Loeb E, Pardue AS, Hill JM
Dept. Immunotherapy, Wadley Inst. Molecular Medicine, 9000 Harry Hines, Dallas, TX, 75235
Dermatologica; 163(2):177-185 1981

Transfer factor potentiates cellular immunity and induces interferon. It was because of these properties that transfer factor was tried in 17 patients with recurrent herpes simplex types 1 and 2. Transfer factor was administered in doses ranging from 5 to 10 U/m2 im. The interval between injections varied from 1 wk to 3 mo. Sixteen patients could be evaluated clinically in whom the recurrence rate decreased from 10.7 +-6.1 to 2.1 +-2.5 (mean SD). The reduction was statistically significant. Eight patients were completely free of disease while the other eight had a reduced number of episodes during the period of observation. Seven patients had abnormal T cell function as reflected by the low number of T cells or low lymphocyte transformation. Statistically significant improvement in the T cell function was observed. Delayed hypersensitivity skin test reactions also improved significantly. (Author abstract) (17 Refs)

69. CHANGES IN ANTITUMOR IMMUNITY AFTER SURGICAL AND CRYOSURGICAL TREATMENT OF TUMOR AND EFFECTS ON NONSPECIFIC IMMUNOSTIMULANTS. EXPERIMENTAL STUDIES USING A RAT TRANSPLANTABLE MAMMARY TUMOR.

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Second Dept. Surgery, Sch. Medicine, Gifu Univ., Tsukasa-cho, Gifu 500, Japan
Gifu Daigaku Igakubu Kiyo; 29(2):228-277 1981

Sprague-Dawley rats in which tumors were induced by a metastasizing rat mammary tumor, MRMT-1, were examined for the effects of surgery, cryosurgery and nonspecific immunostimulants on antitumor immunity. Of the rats in which the tumor was surgically excised 2 wk after inoculation and did not have metastasis, antitumor immunity evaluated by footpad assay showed a peak 4 wk earlier than the rats with unexcised tumors. The nonspecific immunostimulants klebsiellar polysaccharide (PSK), OK-432 and levamisole (LMS) given repeatedly for 1 wk inhibited tumor growth and, except for PSK, lymph node metastasis. In rats in which tumors had been inoculated in the back 2 wk earlier, 81.8% of the regional lymph nodes harbored tumor cells. The incidence of established lymph node metastasis in rats whose tumors had been excised 2 wk after inoculation was 51.6%. Immunostimulants given preoperatively caused no significant change in mortality from metastasis or survival time, but large amounts given postoperatively worsened the disease and reduced footpad reactivity. Splenectomy combined with tumor excision caused further improvement. The effects of therapy were similar in the rats treated by cryosurgery and surgical excision, suggesting that the immun osuppressive effect of an intense cryosurgical insult was counteracted by cryogenically induced immunity. In the early postoperative stage, specific cell-mediated immunity was stronger in the surgical excision group than in the cryosurgery group, while the reverse was true in the late postoperative stage. Antibody-mediated immunity was significantly stronger in the cryosurgery group than in the surgical excision group 1 wk after surgery. (81 Refs) (In JPN)

70. LACTATE DEHYDROGENASE-ELEVATING AGENT IS RESPONSIBLE FOR INTERFERON INDUCTION AND ENHANCEMENT OF NATURAL KILLER CELL ACTIVITY BY INOCULATION OF EHRLICH ASCITES CARCINOMA CELLS INTO MICE.

Koi M, Saito M, Ebina T, Ishida N
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Microbiol Immunol; 25(6):565-574 1981

Ehrlich ascites cells (EAC; 10(6) cells) passaged in the peritoneum of outbred male ddY mice induced interferon (IFN) in the serum with a max of 1,280 antiviral units in the pooled serum/3 mice. A study of properties of the IFN indicated it had characteristics of IFN (stability at pH 2 and lability at 56 C). When splenic cells of mice inoculated with EAC were tested for their natural killer (NK) cell content against YAC-1 target cells, an increase was observed for the first 3 days after inoculation. Plasma lactate dehydrogenase (LDH) was elevated in these mice. Inoculation of ascitic fluid or serum of EAC-bearing mice into normal mice increased plasma LDH activity markedly over normal levels and the elevated activities remained throughout the life of the mice. The possibility that the LDH-elevating agent was responsible for IFN induction was tested by the use of tumor cells which were repeatedly passaged in vitro, a process which eliminates LDH-elevating virus (LDV). Since the inoculation of the passaged cells had no effect on LDH activity (and NK activity) in normal mice, it was concluded that the IFN inducer was LDV which contaminated the EAC and then enhanced the NK activity. N-tropic murine leukemia virus also contaminated EAC, but this virus was not responsible because cultured cells of EAC still shed virus. (25 Refs)

71. GROWTH HORMONE STIMULATION OF NORMAL AND LEUKEMIC HUMAN T-LYMPHOCYTE PROLIFERATION IN VITRO.

Mercola KE, Cline MJ, Golde DW
Div. Hematology-Oncology, Dept. Medicine, Univ. California Los Angeles Center for Health Sciences, Los Angeles, CA, 90024
Blood; 58(2):337-340 1981

In order to investigate the effect of human growth hormone on T lymphocytes, we utilized a clonogenic assay for mitogen-responsive human peripheral blood T lymphocytes. Lymphocytes were purified by density gradient centrifugation and incubated in the presence of phytohemagglutinin using a two-layer agar technique for CFU-T-lymphocyte culture. Nanog concentrations of human growth hormone, ovine prolactin, human chorionic somatomammotropin, or growth hormone fragment were added to cell cultures. Growth hormone potentiated normal T-cell colony formation in a species-specific manner. Cells from a homogeneous T-lymphoblast line derived from a patient with a T-cell variant of hairy cell leukemia also showed augmentation of colony growth in the presence of human growth hormone. These studies provide evidence for a direct effect of growth hormone on normal and some neoplastic human T cells. (Author abstract) (33 Refs)

72. AUGMENTATION OF NATURAL KILLER CELLS INVOLVES BOTH ENHANCEMENT OF LYTIC MACHINERY AND EXPRESSION OF NEW RECEPTORS.

Gustafsson A, Lundgren E
Dept. Clinical Virology, Univ. Umea, S-901 85 Umea, Sweden
Cell Immunol; 62(2):367-376 1981

A good correlation was found between the sensitivity of six hematopoietic cell lines to natural killing by both unstimulated and interferon (IFN)-stimulated effector cells and the ability of these cell lines to induce interferon among human WBC. Two cell lines (HL 60 and P3HR1) were not sensitive to natural killing by unstimulated effectors (less than 10 lytic units) and did not induce IFN. Augmentation of natural killing by preincubation of effector cells with IFN was found to alter the binding of lymphocytes to HL 60 cells but not K 562 cells. This indicates that the augmentation of natural killer cells by IFN involves both enhancement of the lytic machinery and development of new receptors. (Author abstract) (26 Refs)

73. THE REQUIREMENT OF IA-POSITIVE ACCESSORY CELLS FOR THE INDUCTION OF TUMOR-SPECIFIC CYTOTOXIC T LYMPHOCYTES IN VITRO.

Yamashita U, Nakamura H
Dept. Immunology, Univ. Occupational and Environmental Health, Sch. Medicine, 1-1 Iseigoaka, Yahatanishiku, Kitakyushu 807, Japan
Cell Immunol; 62(2):425-435 1981

The mechanism for the induction of cytotoxic T cells specific for tumor-associated antigens was studied by using fractionated responder T cells, tumor cells, and accessory cells in vitro. The tumor-specific cytotoxic T cells were induced by culturing immunized spleen cells with the tumor cells in vitro for 5 days. Nylon-column-purified T cells alone did not induce cytotoxic T cells upon culture with tumor cells, but the addition of normal spleen cells as accessory cells did successfully induce the cytotoxic T cells, suggesting that the presence of accessory cells is required for the activation of tumor-specific cytotoxic T cells in vitro. The accessory function was associated with spleen cell populations adhering to a plastic dish, a Sephadex G-10 column or a nylon wool column, and was sensitive to anti-Ia serum and C treatment, but was resistant to anti-Ig serum or anti-Thy 1 serum and C treatment, suggesting that the accessory cells are Ia-positive macrophages. Not only syngeneic but also allogeneic macrophages had the accessory function and the allogeneic macrophages were also Ia positive. These results suggest that Ia-positive macrophages play a crucial role in the induction of tumor-specific cytotoxic T cells in vitro. The possible role of Ia-positive accessory cells in the induction of tumor-specific cytotoxic T cells is discussed from the standpoint of cellular interactions. (Author abstract) (32 Refs)

74. IMMUNOPOTENTIATING ACTIVITY OF WHOLE CELLS AND MINI-CELLS OF SALMONELLA TYPHIMURIUM.

Kurashige S, Yoshida T, Kodama K, Mitsuhashi S
College Medical Care and Technology, Gunma Univ., Showa-machi, Maebashi, Gunma 371, Japan
Microbiol Immunol; 25(5):467-477 1981

The effect of whole cells of an avirulent strain of Salmonella typhimurium and its mini-cells on humoral immunity, cellular immunity and phagocytosis of macrophages was studied in Balb/c, ICR, and DBA/2 mice. The iv inoculation with both whole cells and mini-cells produced stimulation of phagocytosis of mouse peritoneal macrophages; mini-cells were 1,000x less effective than whole cells. Both whole cells and mini-cells enhanced cell-mediated immunity against leukemia L1210 and sarcoma 180 cells. Whole cells stimulated the antibody-forming cells to produce IgG antibody of higher affinity. Mini-cells stimulated slightly blast cell transformation of lymphocytes from mesenteric lymph nodes of normal mice. (19 Refs)

75. THE GENERATION OF SPECIFIC CYTOTOXIC RESPONSES BY HUMAN LYMPHOCYTES REQUIRES ANTIGEN AND ACTIVITIES PROVIDED BY A LYMPHOKINE SUPERNATANT.

Warren HS
Cancer Res. Unit, Woden Valley Hosp., P.O. Box 11, Woden A.C.T. 2606, Australia
Scand J Immunol; 14(1):71-76 1981

The requirements for the generation of specific cytotoxic responses by human lymphocytes have been investigated using as a model system the response to the UV light-killed mouse tumor P815. These requirements are antigen (P815UV) and activities provided by a human lymphokine (LK) supernatant. Cells that give rise to non-specific cytotoxicity can be separated on discontinuous Percoll density gradients after a 3-day incubation of peripheral blood leukocytes with the lymphokine supernatant, cells from which specific cytotoxic responses can subsequently be generated in the presence of P815UV and LK sediment at a higher density. (Author abstract) (18 Refs)

76. EFFECT OF X-IRRADIATION ON IMMUNOCOMPETENCY OF T-LYMPHOCYTES.

Song CW, Rhee JG, Kim T, Kersey JH, Levitt SH
Dept. Therapeutic Radiology, Radiation Biology Section, Univ. Minnesota Medical Sch., Box 494 Mayo Memorial Building, Minneapolis, MN, 55455
Cancer Clin Trials; 4(3):331-342 1981

The effect of x-irradiation on various aspects of cell-mediated immune reactions is studied. The irradiated splenic lymphocytes could transform to blast cells upon stimulation with PHA, but could not divide into small lymphocytes. It was concluded that irradiation at doses higher than 500 rads inhibits the differentiation of lymphocytes to effector cells upon stimulation with antigens. The irradiated immune lymphocytes were able to kill target tumor cells when the cytotoxicity was tested immediately after irradiation with doses as high as 500 rads. The cytotoxicity of immune lymphocytes diminished, however, 7-10 hr after irradiation. The splenic lymphocytes irradiated with doses as high as 200 rads could stimulate allogeneic lymphocytes 2 days after the irradiation. It thus appeared that irradiation cannot immediately abolish the antigenicity of lymphocytes to stimulate allogeneic lymphocytes. The combined effect of irradiation and T-cell-mediated immune reaction to reduce clonogenicity of target tumor cells in vitro is simply additive. (Author abstract) (46 Refs)

77. INFLUENCE OF MOUSE HEPATITIS VIRUS ON THE GROWTH OF HUMAN MELANOMA IN THE PERITONEAL CAVITY OF THE ATHYMIC MOUSE.

Akimaru K, Stuhlmiller GM, Seigler HF
(c/o Seigler), Duke Univ. Medical Center, Durham, NC, 27710
J Surg Oncol; 17(4):327-339 1981

Mouse hepatitis virus (MHV) infection was found in 15 of 40 athymic mice (BALB/c nu/nu) used in an experimental model designed to study the effect of cell mediated immunity on target human melanoma cells growing in the peritoneal cavity. Most non-MHV-infected mice died of peritoneal tumor within predictable periods following injection of the melanoma cells. Twelve of 15 MHV-infected mice which showed either poor or no tumor growth died of MHV infection, whereas only 3 showed good tumor growth. Peritoneal macrophages in the ascites from the MHV-infected mice were greatly reduced in number compared to those in the ascites from the non-MHV-infected mice. Although the fibrohistiocytic reaction was more prominent in the MHV-infected mice, other aspects of spleen and lymph node lymphocytic reactions exhibited no remarkable differences between the two groups. The possible mechanisms whereby MHV infection influences tumor growth in nude mice are discussed. (Author abstract) (13 Refs)

78. CELLULAR SOURCE OF INTERFERON INDUCED IN HUMAN PERIPHERAL BLOOD MONONUCLEAR LEUKOCYTES BY MUMPS VIRUS OR BY TUMOUR CELLS PERSISTENTLY INFECTED WITH MUMPS VIRUS.

Kato T, Minagawa T
Dept. Microbiology, Hokkaido Univ. Sch. Medicine, Sapporo 060, Japan
J Gen Virol; 54(part2):293-299 1981

Human WBC interferon (IFN-alpha) was induced in cultures of human peripheral blood mononuclear WBC (PBML) from seropositive healthy donors infected by mumps virus, or by a human lung carcinoma cell line (Pc-10) persistently infected with mumps virus (Pc-10/MpV). Adherent cells (Mphi), non-T, non-B cells and B cells all produced IFN in response to mumps virus or Pc-10/MpV cells. The non-T, non-B cel ls co-cultured with Pc-10/MpV cells produced high-titered IFN. However, T cells did not produce any antiviral factors even in the presence of Mphi. Furthermore, T cells activated with phytohemagglutinin (PHA-P), concanavalin A or treated with uv-irradiated mumps virus, or Pc-10/MpV cells pretreated with mitomycin C did not produce any antiviral factors in response to either mumps virus or Pc-10/MpV cells. (Author abstract) (17 Refs)

79. IMMUNE (GAMMA) INTERFERON PRODUCED BY A HUMAN T-LYMPHOBLAST CELL LINE.

Nathan I, Groopman JE, Quan SG, Bersch N, Golde DW
(c/o Golde) Div. Hematology-Oncology, Dept. Medicine, Univ. California Sch. Medicine, Los Angeles, CA, 90024
Nature (Lond); 292(5826):842-844 1981

The characterization of the interferon-gamma (IF-g) produced by a T-lymphocyte cell line (mo) derived from the spleen of a patient with hairy cell leukemia is reported. High IF-g levels were obtained in the presence of fetal calf serum, phytohemagglutinin (PHA), and 12-O-tetradecanoylphorbol-13-acetate; however, in serum-free medium, PHA induction alone gave max IF yield. The Mo IF was of the gamma type by the criteria of acid lability, stimulation of induction, production kinetics, and failure of neutralization by WBC IF antisera. Chromatographic analyses showed that IF-g was a hydrophobic glycoprotein with an apparent mol wt of 40,000. Physiochemically, Mo IF-g was distinct from the erythroid-potentiating activity, colony-stimulating activity, and neutrophil migration-inhibitory factor produced by Mo cells. This cell line should allow the large-scale production of IF-g for purification and clinical trials. (30 Refs)

80. CELL-MEDIATED AND HUMORAL ANTIBODY RESPONSES TO VIRALLY INDUCED TUMOURS.

Walia AS, Lamon EW
Dept. Surgery, Univ. Alabama, Birmingham, AL, 35294
Indian J Med Res; 73:410-419 1981

Thymus-dependent cell-mediated immunity is strongly implicated in resistance to virus induced tumors by the fact that neonatal thymectomy increases the incidence of tumor development even in genetically resistant strains of mice. Evidence is presented in this report that the humoral and cell-mediated arms of the immune response can cooperate at the effector level for the destruction of virus-induced tumor cells. Specific humoral antibodies can cause lymphocytes to be cytotoxic against polyoma and M-MuSV induced tumor cells in vitro. Studies of the mechanism involved in antibody-dependent cell-mediated cytotoxicity have revealed that the effector cells include thymocytes. Cortisone resistant medullary thymocytes are most reactive and both IgM and IgG antibodies induce specific cell-mediated cytotoxicity. (Author abstract) (37 Refs)

81. HETEROGENEITY OF NATURAL KILLER CELLS IN THE MOUSE.

Lust JA, Kumar V, Burton RC, Bartlett SP, Bennet M
Dept. Pathology, Boston Univ. Sch. Medicine, Boston, MA, 02118
J Exp Med; 154(2):306-317 1981

Mice from strains (C57BL/6 x DBA/2)F1 (B6D2F1), B10.D2, CBA/J, C57BL/6J, C57BL/6J-bg/bg (beige), and BALB/c were studied. Mice were injected with heat-killed Corynebacterium parvum (2.1 mg/mouse), cyclophosphamide (300 mg/kg body wt, ip), or 89Sr (100 uCi). Spleen cells were treated with CE anti-CBA, anti-Nk-1.2, serum, and pretested rabbit complement (C). The natural killer cell (NK) activities of spleen cells from mice treated in vivo and of spleen cells treated in vitro were measured against tumor cell lines YAC-1, Cl.18, FLD-3, MPC-11, and WEHI-164.1. NK activities against YAC-1, MPC-11, and Cl.18 tumor cells were significantly reduced in mice treated with 89Sr, spleen cells treated with anti-Nk-1.2 plus C, and beige mice. NK activities against FLD-3 and WEHI-164.1 tumor cells were normal in the same treated groups. The results suggest that two major groups of

NK cells are present in mouse spleen suspensions. NK-A cells are marrow-dependent, Nk antigen positive, and lacking in beige mice. They are effective against YAC-1, MPC-11, and Cl.18 tumors. The NK-B cells are marrow-independent, NK antigen negative, and present in beige mice. They are effective against WEHI-164.1 and FLD-3 tumors. The NK-B group is apparently made up of subgroups with varying susceptibility and ages of maturation. (28 Refs)

82. STUDY OF IMMUNODEPRESSIVE EFFECT OF ANTHRACYCLINE ANTIBIOTICS IN TWO DIFFERENT MODELS OF TRANSPLANTATION IMMUNITY.

Liashenko VA, Shapovalova SP, Aleksander SK
All-Union Res. Inst. Screening for New Antibiotics, Moscow, USSR
Antibiotiki; 26(7):546-549 1981

Comparative immunodepressive effect of anthracycline antibiotics carminomycin (CM) and rubomycin (RM) was evaluated by rejection of the allogeneic skin graft and by graft vs host reaction (GVHR). Experiments were carried out in CBA and BALB/c mice. CM at 0.3 LD50 increased duration of survival of the skin graft by 8.8 days, compared with a 2.5-day increase after RM administration at 0.3 LD50. CM reduced lethality of recipient mice in GVHR, while RM was ineffective. It was concluded that CM provided effective inhibition of stimulated precursors of T-killer cells. (4 Refs) (In RUS)

83. EFFECT OF THE NEW IMMUNOSUPPRESSIVE AGENT, CYCLOSPORIN-A, ON NATURAL KILLER CELL AND ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXIC ACTIVITY.

Attallah AM, Urritia-Shaw A, Yeatman TJ, Folks T
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Int Arch Allergy Appl Immunol; 65(4):465-469 1981

Athymic nude mouse homozygotes (nu/nu) and the heterozygote nu/nu+ were injected ip with 2 mg of cyclosporin-A (CS-A) twice, 72 and 1 hr prior to analysis. We have found that in vivo administration of CS-A results in a significant suppression of natural killer (NK) cell and antibody-de pendent cell-mediated cytotoxic (ADCC) activity which probably play an important role in tumor and graft rejection. T cells were also suppressed, in contrast, B cells were found to be immunocompetent as determined by cell proliferation and antibody-forming capacity in response to mitogens and antigens. The identity of cells mediating NK cell and ADCC activity and its relationship to T lymphocytes are also discussed. (Author abstract) (10 Refs)

84. MAJOR H-2 AND NON-H-2 DIFFERENCES BETWEEN PARENTAL STRAINS PREVENT OCCURRENCE OF FETECTOMY-INDUCED YOLK SAC TERATOMAS.

Muranyi-Kovacs I, De Lapeyriere O, Courcoul MA, Arnaud D
Unite 119 de L'INSERM, 27, Bd Lei Roure, 13009 Marseille, France
Transplantation; 32(2):142-148 1981

The questions of whether H-2 and/or non-H-2 differences are responsible for the rejection of allogeneic teratomas and whether serological and cellular maternal immune reactions can be demonstrated by in vitro assays, were addressed. Fetectomies were performed in female mice mated with syngeneic, congeneic, or allogeneic males and the animals were killed at 4, 6, and 8 wk or exceptionally at 3 mo after fetectomy. Benign teratomas comprising multiple tissue formations, derived from all three germinal layers, were observed only in syngeneic pregnancies. These induced teratomas were less frequent in some strains (A/Xn, A-By, and A-SW) than in others (A-CA, B10-A, C57Bl/6 and C3H/He). It was shown that minor or major histocompatibility differences between the parental strains, and thus between the mother and fetuses, were sufficient to prevent the occurrence of hybrid teratomas. Only cartilaginous outgrowth could be observed on the uteri of females mated with nonsyngeneic males. The serological activities observed in the fetectomized females were elicited by the fetectomy rather than the pregnancy. A cell-mediated maternal reaction against alien paternal antigens was demonstrated in fetectomized females by an in vitro assay. It was determined that the cell-mediated cytotoxicity observed in fetectomized females was induced by fetectomy. These results suggest that a maternal immune reaction is not efficiently altered by the normal first half of pregnancy and that differentiated teratoma tissues express the paternal antigens sufficiently to induce their immune rejection. (46 Refs)

85. CYTOTOXIC CELLS INDUCED IN VITRO BY EPSTEIN-BARR VIRUS ANTIGENS.

Hutt-Fletcher LM, Gilbert CJ
Dept. Bacteriology and Immunology, Cancer Res. Center, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Cell Immunol; 63(1):91-105 1981

Lymphocyte blastogenesis and cytotoxicity for lymphoid cells line (LCL) were induced in cells from immune donors by stimulation in vitro with irradiated Epstein-Barr Virus (EBV). Velocity sedimentation of blastogenic populations indicated that much of the killing was associated with l arge E-rosetting cells; it was reduced by [3H]thymidine suicide immediately prior to sedimentation. Target cells were killed irrespective of EBV content or sensitivity to natural killer (NK cells), though the pattern of lysis varied with repeated use of individual donors. Up to 9% of the normal resting lymphocytes became blastogenic though fewer than 30% of the dividing cells at termination of culture had undergone more than one division. It is suggested that EBV antigens induce a polyclonal activation of cytotoxic T cells. The possible significance of this response is discussed with particular reference to the origin of non-EBV-specific cytotoxic blast cells in infectious mononucleosis. (Author abstract) (46 Refs)

86. IMMUNOPREVENTION OF FRIEND VIRUS-INDUCED ERYTHROLEUKEMIA BY VACCINATION WITH VIRAL ENVELOPE GLYCOPROTEIN COMPLEXES.

Hunsmann G, Schneider J, Schulz A
Forschergruppe Tumorimmunologie, D-7800 Freiburg, W. Germany
Virology; 113(2):602-612 1981

Adult STU mice were repeatedly immunized with aggregates of Friend virus envelope glycoprotein gp85. The antigen was given emulsified in incomplete Freund's adjuvant. After the last boost, animals were challenged with a dose of FLV inducing fatal erythroleukemia in 90-100% of the controls. Twenty of 20 mice immunized with 100 ug of gp85 were completely protected, while 3 of 7 animals vaccinated with 10 ug of gp85 died of leukemia. Smaller doses were ineffective, as was the adjuvant alone. Only animals that had developed a strong antibody response survived the FLV challenge. Serum antibodies of these animals reacted with type-, species-, and interspecies-specific determinants of pg85. Only a marginal cellular reactivity to gp85 was detected. The development of viremia was monitored by the use of radioimmunoassay for the internal viral core polypeptide p30. Animals completely protected were not viremic later than 7 days post-FLV infection. Those mice of the immunized groups which died in spite of an early antibody response showed a sharp decrease in serum antibodies to gp85 and a simultaneous appearance of virus in blood about 2-4 wk before death from leukemia. Thus, the suppression of virus spread by antibody seems to be important for immuno-prevention of this virus-induced leukemia. (Author abstract) (26 Refs)

87. IMPAIRMENT OF IN VITRO GENERATION OF CYTOTOXIC OR T SUPPRESSOR LYMPHOCYTES BY FRIEND LEUKEMIA VIRUS INFECTION IN MICE.

Garaci E, Migliorati G, Jezzi T, Bartocci A, Gioia L, Rinaldi C, Bonmassar E

Inst. Microbiology, Univ. Rome, Piazzale Aldo Moro, 00100 Rome, Italy

Int J Cancer; 28(3):367-373 1981

Spleen cells collected from DBA/2 (H-2d) mice inoculated with the polycythemic variant of Friend-Leukemia Virus Complex (FLV-P) were tested for T-dependent immune functions such as the in vitro generation of cytotoxic T lymphocytes (CTL) and of non-specific T suppressor lymphocytes (STL). CTL were generated against H-2b splenocytes, and STL were obtained following a 5-day lymphocyte culture without stimulator cells. A progressive and severe impairment of the generation of both CLT and STL was found from 2 wk onward after infection, being almost totally abolished 3-4 wk after virus challenge.. Suppressor cells (SC) capable of inhibiting CTL generation were detected in FLV-P bearing mice. Suppressor activity was unaffected by anti-Thy 1.2 serum and complement but was removed following iron-magnet depletion or passage through nylon-wool column. Moreover complete recovery of the competence of CTL generation was attained when FLV-P infected splenocytes were passed through nylon-wool column. It is concluded that FLV-P infection depresses T-dependent cytotoxic and suppressor responses in mice, by the appearance of non-T adherent phagocytic cells, capable of impairing CTL generation in vitro. (Author abstract) (39 Refs)

88. 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) TREATMENT ELEVATES THE NATURAL KILLER (NK) SENSITIVITY OF CERTAIN HUMAN LYMPHOID LINES.

Patarroyo M, Biberfeld P, Klein E, Klein G

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Cell Immunol; 63(2):237-248 1981

The natural killer (NK) sensitivity of two Epstein-Barr virus (EBV)-carrying Burkitt lymphoma lines (Daudi and Raji) and one EBV-negative lymphocytic leukemia-derived T-cell line (Molt-4) increased when they were cultured for 24 hr in the presence of the phorbol ester TPA. In the EBV-carrying lines, this increase occurred independently of the entry of the cells into the viral cycle. 12-O-Tetradecanoylphorbol-13-acetate (TPA)-treated Daudi and Molt-4 cells cross-competed for the effectors in the NK assay as indicated by the cold-target inhibition tests. TPA-treated cells showed an increased binding of human but not of mouse lymphocytes. (Author abstract) (19 Refs)

89. STIMULATORY EFFECTS ON VARIOUS IMMUNOLOGIC RESPONSES BY ASCITES FLUIDS FROM PATIENTS WITH METASTATIC MALIGNANCY.

Wang BS, Heacock EH, Collins KH, Saporoschetz I, Steele G, Mannick JA

Dept. Surgery, Brigham and Women's Hosp., Harvard Medical Sch., Boston, MA, 02115

Clin Immunol Immunopathol; 21(1):83-93 1981

Cancer ascites has been repeatedly shown to suppress a number of immune responses. In this report, we examined a total of 28 unfractionated ascitic fluid samples from patients with various metastatic malignancies and rather unexpectedly found that the majority of these samples were capable of enhancing various immune reactivities. Twelve of 17 samples were shown to increase significantly humoral antibody production in mice when injected 1 day before sheep RBC. Ten of 13 samples significantly enhanced the proliferative response of human peripheral blood mononuclear WBC to the T-lymphocyte mitogen, phytohemagglutinin. Twelve ascitic samples were added to mouse mixed lymphocyte cultures and 9 were found to augment significantly the generation of alloreactive cytolytic lymphocytes. Pooled normal human serum was similarly tested as a control and found to have no effect in these systems. Furthermore, we have isolated three active fractions from these cancer ascites fluids by Sephadex G-75 gel filtration. However, each fraction was predominantly responsible for enhancing only one of the three immune responses tested. (Author abstract) (16 Refs)

90. IMMUNOSUPPRESSION BY 2'-DEOXYCOFORMYCIN: STUDIES ON THE MODE OF ADMINISTRATION.

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Cell Immunol; 63(2):259-271 1981

It was previously reported that continuous infusion of 2'-deoxycoformycin (DCF), a potent inhibitor of the enzyme adenosine deaminase (ADase), produces a severe immunodeficiency of both T and B lymphocytes. In the present study the immunological and biochemical effects in C57BL/6J mice of daily single ip injections of DCF are examined. Five days of daily injections of DCF at 0.4 mg/kg body wt/day produced both immunosuppression and lymphocytotoxicity. Parallel experiments indicated that continuous infusion of DCF at the lower dose of 0.3 mg/kg body wt/day resulted in a more potent depression of immune function and a greater lymphocytotoxicity. In particular we have observed after single injections: (i) A decrease in body wt of 4.7%, compared to 16.2% after continuous infusion; (ii) a decrease in differential lymphocyte count from 90.3% (normal) to 65.6%, compared to 31.4% after continuous infusion, and a decrease in WBC count (per mm2) from 5,200 (normal) to 3,800, compared to 2,300 after continuous infusion, while no difference in other blood parameters, including RBC number, hematocrit, and Hb concentration, was observed, (iii) on histological examination, a depletion of T and, to a lesser extent, B lymphocytes, and an atrophy of lymph nodes, spleen, and thymus; and (iv) significant depression in blastogenesis induced by the T-cell mitogens concanavalin A and phytohemagglutinin and, to a lesser extent, by the B-cell mitogen Escherichia coli lipopolysaccharide. ADase was inhibited to a high degree ranging from 84 to 94% in lymphoid organs and RBC from animals receiving DCF by either mode of administration. These data provide further direct support for the importance of ADase to proper lymphocyte function, and suggest that continuous infusion may be the preferred mode of administration in clinical trials of DCF as an antileukemic agent. (Author abstract) (39 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

91. ENHANCEMENT OF MACROPHAGE TUMORICIDAL CAPACITY BY LIPOSOMES.

Jeannin JF, Olsson NO, Martin F
Laboratoire d'Immunologie, CNRS: ERA 628, INSERM: U45, Faculte de Medecine, 21033 Dijon, France
C R Soc Biol (Paris); 175(3):342-346 1981

The effects of phosphatidylcholinedipalmitoyl (DPPC) and lysophosphatidylcholinepalmitoyl (LPCP) liposomes on the lysis of DHD K12 cancer cells, derived from a colon adenocarcinoma of BD IX rats, by syngeneic BCG-activated macrophages in vitro were determined. DPPC liposomes increased the cytolytic effect observed in experiments, while LPCP liposomes showed no effect on the activity of activated macrophages. (8 Refs) (In FRE)

92. SJL TUMOR: A NEOPLASM INVOLVING MACROPHAGES.

Ford RJ, Ruppert B, Maizel AL
Dept. Pathology, M. D. Anderson Hosp. and Tumor Inst., Texas Medical Center, Houston, TX, 77030
Lab Invest; 45(2):111-119 1981

Tumor-bearing lymph nodes from SJL mice were characterized by histologic, ultrastructural, and immunologic methods. These approaches consistently revealed a predominance of macrophage-like cells in the primary neoplasm. When the tumor-bearing lymph nodes were placed in cell culture, colonies of adherent cells grew slowly to confluence and demonstrated morphologic and functional properties of macrophages. The tumor cells were also grown in soft agar where clusters and colonies of large, often binucleate, cells predominated. These cells were uniformly nonspecific esterase-positive, again, suggesting a macrophage origin. In addition, supernatants derived from SJL tumor cells were shown to have mitogen-augmenting activity as tested on murine thymocytes. These findings are discussed in the context of the SJL tumor as a proliferative condition primarily involving macrophages, which may be useful as a model of human diseases such as Hodgkin's disease. (Author abstract) (40 Refs)

93. SPECIFICITY OF FC RECEPTORS FOR IGG2A, IGG1/IGG2B, AND IGE ON RAT MACROPHAGES.

Boltz-Nitulescu G, Bazin H, Spiegelberg HL
Dept. Immunopathology, Res. Inst. of Scripps Clinic, La Jolla, CA, 92037
J Exp Med; 154(2):374-384 1981

Alveolar and peritoneal macrophages (M-phi) were obtained from Lewis and Brown Norway rats. The ability of M-phi to form rosettes with fixed ox RBC (Eo') coated with myeloma proteins of all Ig classes, and with fresh RBC (Eo) sensitized with rat IgG1 and IgG2, rabbit IgG and IgM, and mouse antibodies was measured. Rosettes were formed with Eo' coated with IgG1, IgG2a, IgG2b, and IgE myeloma proteins, but not with IgG2c, IgA, IgM, or IgD. Rosettes were also formed with Eo' coated with human IgG1, IgG3, IgG4, mouse IgG1, IgG2a, IgG2b, and rabbit IgG. Rosettes were formed with Eo sensitized with rat IgG1, IgG2, or rabbit IgG. No rosettes were formed with rabbit IgM or mouse IgA. M-phi treated with trypsin formed rosettes with IgG2a, but not with IgG1, IgG2b, or IgE. The IgG2a and IgE rosettes were inhibited only by rat IgG2a and IgE, respectively, indicating that they were class specific. IgG1 and IgG2b were not class specific. Apparently rat M-phi have at least three types of Fc receptors: (1) a rat IgG2a-specific, trypsin resistant receptor, (2) a rat IgE-specific, trypsin-sensitive receptor, and (3) a rat IgG1, IgG2b, and heterologous IgG-sensitive, trypsin sensitive receptor. (49 Refs)

94. POST-OPERATIVE INHIBITION OF MACROPHAGE INFLAMMATORY RESPONSES.

Normann SJ, Schardt M, Cornelius J, Sorkin E
Dept. Pathology, Coll. Medicine, Univ. Florida, Box J-275, Gainesville, FL, 32610
J Reticuloendothel Soc; 30(2):89-97 1981

Partial hepatectomy, unilateral nephrectomy, and hind limb amputation inhibited macrophage but not PMN accumulation at inflammatory sites. Macrophage accumulation was inhibited in the peritoneal cavity and sc tissues by the three surgical procedures and in the pleural space by partial hepatectomy. The anti-inflammatory effect of major surgery had certain interesting similarities to that caused by cancer in being cell selective, unrelated to altered macrophage adherence, present despite an adequate number of macrophage precursors, and passively transferable with serum. (Author abstract) (14 Refs)

95. INFLAMMATION AND TUMOR GROWTH. I. TUMOR GROWTH IN MICE WITH DEPRESSED CAPACITY TO MOUNT INFLAMMATORY RESPONSES: POSSIBLE ROLE OF MACROPHAGES.

Nelson M, Nelson DS, Hopper KE
Kolling Inst. Medical Res., Royal North Shore Hosp., St. Leonards NSW 2065, Australia
Am J Pathol; 104(2):114-124 1981

Studies were made of the effects of various treatments on the growth in mouse feet of isografts of two methylcholanthrene-induced fibrosarcomas: C-4, of CBA/J mice, and A-2, of A/J mice. The isografts were prepared by pronase digestion of sc tumors and were injected as unseparated cell suspensions or as tumor-cell-enriched suspensions after depletion of infiltrating host inflammatory cells. The recipient mice were untreated or treated with reserpine, sublethal whole body irradiation, cyclophosphamide, or corticosteroids. Depletion of host cells from the inoculum resulted in increased growth from the same number of tumor cells. Reserpine treatment decreased the growth of both tumors, whether unseparated or tumor-cell-enriched, and whether injected into the foot or the flank. Irradiation, cyclophosphamide pretreatment, and corticosteroid pretreatment decreased the growth of normal inocula or enriched inocula or both. The effects of cyclophosphamide and corticosteroids were apparently not due to cytotoxicity to tumor cells. Normal resident peritoneal cells increased tritiated thymidine uptake by tumor cells in vitro. Sedimentation velocity separation showed the largest cells to be the most potent . It is suggested that some host inflammatory reaction is necessary for optimal tumor growth and that murine hosts produce not only cells with antitumor effects but also cells, possibly a subpopulation of macrophages, that potentiate tumor growth. (Author abstract) (54 Refs)

96. INHIBITION OF MACROPHAGEAL TRANSFORMATION OF MONONUCLEAR CELLS OF PERIPHERAL BLOOD IN BREAST CANCER.

Dzhaginiian AI, Demchenko TA
Medical Inst. Sanitation and Hygiene, Leningrad, USSR
Vopr Onkol; 27(6):32-35 1981

Macrophageal transformation of mononuclear cells of peripheral blood was evaluated quantitatively in vitro. The study group included 60 patients with breast cancer Stage II-IV and 50 healthy subjects. Transformation of mononuclear cells to macrophages in breast cancer patients, particularly in advanced cases, was found to be reduced, as compared with healthy controls. The serum of cancer patients contains an inhibitor of this process. This was confirmed by mononuclear cell transformation being inhibited both in patients and controls on addition of the serum of cancer patients to both cultures. The function of tumor patients' cells was partially restored, when serum of healthy controls was added. It is suggested that macrophageal transformation be used as a test for immunologic examination of tumor patients. (Author abstract) (13 Refs) (In RUS)

97. MURINE MACROPHAGE CYTOTOXICITY INDUCED BY MASTOCYTOMA CELLS, CELL-FREE MASTOCYTOMA EXUDATES, AND EXTRACTS.

Dullens HF, Den Otter W
Dept. Pathology, Utrecht Univ., Pasteurstraat 2, 3511 HX Utrecht, The Netherlands
Immunopharmacology; 3(3):241-251 1981

The induction of macrophage cytotoxicity against nonrelated tumor target cells when the test and target cells were incubated with mastocytoma P815 ascitic fluid and or P815 cell extracts was examined using BALB/c, CBA, C57BL/10, and DBA/2 male and female mice as sources of peritoneal macrophages and cells from the following tumors: SL2, L5178Y, and EL4 lymphosarcomas; TLX9 thymoma; and P815 mastocytoma. CBA macrophages expressed significant cytotoxicity against DBA/2-derived P815 mastocytoma cells but not against DBA/2-derived SL2 cells or against C57BL/10-derived TLX9 or EL4 cells. The CBA macrophages also expressed some cytotoxicity against the DBA/2-derived L5178Y cells. When CBA macrophages were incubated with ip-grown P815 cell-free exudate, cytotoxicity against SL2 and EL4 cells was observed. When SL2 cells were incubated with P815 ascitic fluid before the tumor cells were added to monolayers of CBA macrophages, SL2 cell growth on these monolayers was inhibited. Two treatments were capable of abolishing macrophage cytotoxicity: incubation with ascitic fluid or with tumor extract, followed in either case by trypsinization and then challenge with tumor cells. Trypsinization alone did not effect this loss of activity. Cytotoxicity remained inducible after 7 days' storage of the exudate at-5 C, but was lost after 72 hr of storage at room temperature; storage at-20 C had no effect. The effect is due to a small-mol wt, dialyzable factor of mol wt less than 1,000, according to the results of gel filtration of the cell-free exudate. This factor was not demonstrated in the supernatant of P815 cells unless the cultures contained 40% or more dead cells. Further characterization of the factor and its possible application in therapeutics are under way. (23 Refs)

98. GROWTH STIMULATION OF EWING SARCOMA AFTER MACROPHAGE INHIBITION IN ATHYMIC NUDE MICE.

Torhorst J
Institut fur Pathologie, Universitat, Schonbeinstrasse 40, CH-4003 Basel, Switzerland
Schweiz Med Wochenschr; 111(36):1319-1321 1981

Inoculation of cell suspensions of a Ewing sarcoma (1.5 to 2.0 x 10(8) viable cells/mouse) into thymusless nude mice bred under conventional conditions gave a 90% take rate after sc injection and 35% after ip. Ip take rate is raised to 90% by ip pretreatment with India ink. The same pretreatment shortens the tumor doubling time after sc inoculation. Both events are probably caused by inhibition of macrophages and/or natural killer cells. (Author abstract) (27 Refs) (In GER)

99. THE INFLUENCE OF HOST HEALTH AND ENVIRONMENT ON NATURAL CYTOTOXICITY OF MOUSE MACROPHAGES.

Fidler IJ, Davis TW, Raz A
Dept. Cell Biology, The Weizmann Inst. of Science, P.O. Box 26, Rehovot 76 100, Israel
Cancer Immunol Immunother; 11(3):195-199 1981

C3H/HeN and C57BL/6N male and female inbred mice, derived by hysterectomy and maintained under barrier conditions, were injected ip with 2 ml thioglycollate broth (TG), 1 mg concanavalin A (conA), or bactopeptone (BP). Other groups received BCG (10(7) viable organisms/mouse) or 0.5 ml complete Freund's adjuvant (CFA), in each case followed 10 days later by 2 ml TG. Macrophages were harvested from the mice by peritoneal lavage. Tumoricidal activity (TA) of the macrophages was measured in vitro using B16F10 melanoma or UV-2237 fibrosarcoma cells. No TA was shown by macrophages from untreated mice or from mice in which inflammation had been induced by TG, conA, or BP. Infection caused by BCG or CFA or stressful (crowded) conditions induced TA in the macrophages. In mice whose macrophages were already activated, no further activation was possible. Evidently the natural cytotoxicity of mouse peritoneal macrophages against tumor cells in vitro is influenced by the health and environment of the host. Use of hysterectomy-derived, barrier-maintained mice is advised in studies of macrophage activity to prevent generation of spontaneously cytotoxic macrophages. (34 Refs)

100. ADRIAMYCIN-ACTIVATED MACROPHAGES AS TUMOR GROWTH INHIBITORS.

Haskill JS
Dept. Obstetrics and Gynecology, Univ. North Carolina, 620, F. L. O. B. Building , Chapel Hill, NC, 27514
Cancer Res; 41(10):3852-3856 1981

Flow cytometry has been used to study the influence of Adriamycin- and Corynebacterium parvum-elicited cytostatic macrophages on the cell cycle of HeLa cells. Macrophages harvested from the peritoneal cavity of mice given ip injections of Adriamycin retain cytostatic activity for 3 to 4 days in vivo. Many of these macrophages fluoresced with the red emission spectra characteristic of Adriamycin. The decline in the presence of macrophages exhibiting red fluorescent cytoplasmic particles paralleled the loss in cytostatic activity. Drug-induced cytostatic macrophages exhibited at least as high a level of growth inhibition as did C. parvum-activated cells. In contrast to the apparent G1 block of HeLa cells which resulted from interaction with C. parvum-activated macrophages, Adriamycin-stimulated macrophages inhibited growth in the G2-M phase characteristic of the free drug. Multiple freeze-thaw cycles removed all activity from C. parvum macrophages but had no influence on the adriamycin-elicited effector cell activity. The data suggest that in vivo drug storage by macrophages may represent an important step in tumor cell destruction by Adriamycin. (Author abstract) (16 Refs)

101. MALEIC VINYL ETHER ACTIVATION OF MURINE MACROPHAGES AGAINST LUNG-METASTASIZING TUMORS.

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Cancer Res; 41(10):3901-3906 1981

A.M.W. 15,500 fraction of maleic vinyl ether (MVE-2) induced tumoristatic and tumoricidal activity in peritoneal macrophages of BALB/c and C57BL/6 mice following ip administration. Growth of B16 melanoma cells in vitro was inhibited up to 85% by MVE-2-activated, but not resident, peritoneal macrophages. In a tritiated thymidine release assay, B16 melanoma cells, and to a lesser extent Madison 109 lung carcinoma cells, were also sensitive to the cytolytic action of MVE-2-activated peritoneal macrophages. Administration iv of MVE-2 resulted in tumoristatic and tumoricidal activity in alveolar macrophages against radiolabeled B16 and Madison 109 lung carcinoma target cells. MVE-2-activated alveolar macrophages significantly inhibited L5178Y lymphoma colony formation following a 48-hr macrophage-tumor coincubation. BALB/c mice bearing the lung-metastasizing Madison 109 lung carcinoma footpad tumor were given MVE-2 iv, using the same dosing regimen that induced alveolar macrophages to be tumoricidal in vitro. Significant increase in life span were observed, suggesting that the antitumor activity of MVE-2 in this tumor system may be mediated by the activation of alveolar macrophages, with a resulting decrease in metastatic growth in the lung. (Author abstract) (30 Refs)

102. SIMPLE ESTIMATION OF MACROPHAGE ACTIVITY IN TUMOUR-BEARING ANIMALS TREATED WITH CORYNEBACTERIUM PARVUM.

Wilson RG

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Br J Exp Pathol; 62(4):347-349 1981

The effects of Corynebacterium parvum on the reticuloendothelial system and on tumor growth have been known for many yr. The causes of these effects have been the subject of many hypotheses and we here discuss a new method of evaluating macrophage activity and some of its components. These studies show that in macrophage activation the degree of enzymic activity and the cell size are more important than the number of cells present and that by giving silica concurrently it is macrophage enzyme activity and cell size that one affects and not cell number. Consequently, it is of no use simply to count macrophages in a section in studies of this system. (Author abstract) (8 Refs)

103. IN VIVO INHIBITION OF THE DEVELOPMENT OF MYELOID LEUKEMIA BY INJECTION OF MACROPHAGE- AND GRANULOCYTE-INDUCING PROTEIN.

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Dept. Genetics, Weizmann Inst. Science, Rehovoth 76100, Israel

Int J Cancer; 28(3):375-386 1981

Injection of macrophage- and granulocyte-inducing protein (MGI) can inhibit the development of myeloid leukemia in vivo and stimulate normal myelopoiesis. The MGI injected contained MGI-1 activity that induces colony formation with normal myeloblasts, and MGI-2 activity that induces differentiation of normal and MGI 7+ 1D 7+ 1 leukemic myeloblasts to mature macrophages or granulocytes. Injection of MGI reduced the tumor vol in mice sc inoculated with leukemic cells at least 50-fold The median survival time of MGI 7+ 1D 7+ 1 cells or sc with MGI 7+ 1D 7-1 cells was increased by about 40%, and 50% of the MGI-treated mice inoculated sc with MGI 7+ 1D 7+ 1 cells did not develop tumors. MGI also increased the anti-tumor effect of cyclophosphamide. The leukemia-inhibiting activity in the injected MGI preparations was associated with the peak of MGI activity separated on a hydroxylapatite column and was destroyed by treatment at the temperature which destroys MGI-2 activity. This indicates that the inhibition of leukemia development was mediated by MGI-2. It is suggested that improved schedules of MGI treatment, with or without compounds used in the cytotoxic types of therapy, should be able to give an even better inhibition of leukemia development and that these results should also be applicable to the therapy of human myeloid leukemia. (61 Refs)

104. PRODUCTION OF INTERFERON BY AN SV40-TRANSFORMED MACROPHAGE LINE, BB-W-531-2.

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Dept. Bacteriology, Tottori Univ., Sch. Medicine, Yonago, Tottori 683, Japan

Microbiol Immunol; 25(7):683-692 1981

Interferon (IF) production during the phenotypic transition between the nonmacrophage and macrophage states of Simian virus-40 (SV40)-transformed cells was examined. The ability of SV40-tr ansformed cells to produce IF following treatment with various viral and nonviral inducers was studied. Stationary SV40-transformed macrophages (BB-W-531-2 BALB/cAnN mouse cells) culture-split and cultivated on tissue culture dishes (SP method) produced IF without exogenous stimulation, although only in the growing phase and not in the stationary phase. Stationary transformed cells grown on bacteriologic dishes (BP method) or growing cells grown on tissue culture dishes (SGP method) did not produce a significant level of IF throughout the culture period. When the cells that were subcultured by the BP method were treated with various inducers (penicillin-attenuated Streptococcus pyogenes, lipopolysaccharide, and polyinosinate-polycytidylate), large quantities of IF were produced. Cells subcultured according the SGP method produced no significant IF after identical exposure to inducers. The IF induction in cells subcultured according to the BP method following lipopolysaccharide administration was dose dependent. The characteristics of the BB-W-531-2 cell-produced IF-like substance are described. The results suggested that the ability of BB-W-531-2 cells to produce IF is associated with the expression of several macrophage properties. (20 Refs)

105. SUPPRESSION OF LYMPHOKINE PRODUCTION: II. MACROPHAGE-DEPENDENT INHIBITION OF PRODUCTION OF MACROPHAGE ACTIVATING FACTOR.

Varesio L, Holden HT, Taramelli D
NCI, Frederick Cancer Res. Center, Frederick, MD, 21701
Cell Immunol; 63(2):279-292 1981

The ability of different populations of macrophages to affect the production of macrophage activating factor (MAF) by stimulated T lymphocytes was investigated. We found that activated macrophages, infiltrating MSV-induced regressing tumors or macrophages recovered from the peritoneum of mice injected with Corynebacterium parvum, were able to actively suppress the production of MAF. MAF production by antigen-stimulated MSV-immune or alloimmune spleen cells and by normal spleen cells stimulated by Con A was susceptible to macrophage-dependent suppression to a similar extent. In contrast, resident macrophages or those elicited by light mineral oil or proteose-peptone did not affect MAF production. While suppressor macrophages added at the time of the lymphocyte stimulation inhibited MAF production, the same cells added 4-6 hr after stimulation were ineffective. Therefore, it seems that the macrophages suppressed the early events of lymphocyte activation leading to MAF production. Suppressor macrophages, by inhibiting MAF production, may limit the expansion of the cytotoxic activity. This regulation of macrophage functions, mediated by the effects of suppressor macrophages on T lymphocytes, could be responsible for an insufficient antitumor cytotoxic response by macrophages. (Author abstract) (52 Refs)

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY

106. INCREASED SENSITIVITY OF LYMPHOCYTES FROM PATIENTS WITH HODGKIN'S DISEASE TO CONCANAVALIN A-INDUCED SUPPRESSOR CELLS.

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J Immunol; 127(3):1216-1220 1981

We have studied both the capacity of lymphocytes from patients with active Hodgkin's disease to generate suppressor cells when they are stimulated with concanavalin A (Con A) and the sensitivity of these lymphocytes to the suppression exerted by normal lymphocytes that had been induced with Con A. Lymphocytes were incubated in the presence or absence of Con A, 50 ug/ml, for 48 hr and treated with mitomycin C. Their regulatory activity on the proliferation of fresh allogeneic lymphocytes stimulated by a suboptimal (10 ug/ml) dose of Con A was assayed in a second culture. We found no significant difference between the suppressive activity induced by Con A in lymphocytes from normal individuals (40.1 +-3.2%) and 13 patients with active Hodgkin's disease (35.0 +-3.2%; p greater than 0.12). The proliferative response of the lymphocytes from 20 patients with active, untreated Hodgkin's disease was much more sensitive to the inhibition exerted by normal, allogenic, Con A induced suppressor cells (59.4 +-3.2%) than that of lymphocytes of 30 normal controls (39.8 +-2.4%; p less than 0.001). The sensitivity to suppression was greater in patients with advanced stage of disease (70.4 +-4.8%) than that observed in both normal controls (p less than 0.001) and patients with early stages (53.5 +-3.2%; p = 0.01); the patients with early stages were still significantly more sensitive to suppression than the normal controls (p less than 0.01). The difference in sensitivity to suppression was not caused by the lower proliferation of patients' lymphocytes in response to Con A, since identical results were obtained when normals with low Con A-induced proliferation were selected for comparison. Indomethacin in the second culture did not reverse the suppression, nor did depletion of adherent cells from the responders' lymphocytes. Suppression required the presence of living suppressor cells early in the second culture. Active suppressor cells did not remove Con A from the second culture, nor did they kill the responding lymphocytes. Thus, although lymphocytes of patients with active Hodgkin's disease develop normal suppressor cell activity in response to Con A, they have excessive sensitivity to suppression by Con A-induced regulatory cells. Increased sensitivity to T cell regulation may explain some of the T cell deficits observed in patients with Hodgkin's disease. (Author abstract) (33 Refs)

107. EVIDENCE FOR INTERACTION BETWEEN T CELL POPULATIONS OF TUMOR-BEARING AND NORMAL MICE IN IMMUNE SUPPRESSION.

Ingenito GG, Calkins CE
Dept. Microbiology, Thomas Jefferson Univ., 1020 Locust St., Philadelphia, PA, 19107
J Immunol; 127(3):1236-1240 1981

Spleen cells of DBA/2 mice bearing sc implants of the syngeneic tumor L5178Y induce suppression of the in vitro antibody response of normal spleen cells to sheep RBC (SRBC). Cells mediating suppression are detected in the spleens of tumor-bearing mice as early as 24 hr post-implantation but are no longer detected there 15 days post-implantation. These spleen cells are nylon wool nonadherent, sensitive to anti-Thy 1.2 + C and anti-Lyt 1.1 + C, and insensitive to anti-Lyt 2.1 + C treatment. The anti-SRBC response of the unfractionated spleen cells from the tumor-bearing mice is not itself suppressed at the cell numbers used. This along with the finding that suppression occurs in the presence of spleen cells from normal mice suggest that a cell population from the normal mouse spleen is also involved in the suppression. Spleen cells from mice inoculated with irradiated (nonproliferating) L5178Y cells are similarly capable of mediating nonspecific suppression for the same limited period of time after the inoculation. In addition, spleen cells from mice stimulated with several nontumorigenic cellular antigens interact with normal spleen cells to produce suppression. These findings suggest that suppression observed in vitro with spleen cells from these tumor-bearing mice may be the result of antigen-activated cells triggering normal immunoregulatory cells. (Author abstract) (30 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

108. LOSS OF TUMOR-SPECIFIC AND IDIOTYPE-SPECIFIC IMMUNITY WITH AGE.

Flood PM, Urban JL, Kripke ML, Schreiber H
La Rabida-Univ. Chicago Inst., Univ. Chicago, Chicago, IL, 60637
J Exp Med; 154(2):275-290 1981

Two fibrosarcomas, 1591 and 1316, were induced in C3H/HeN mice by exposure to UV. Both types were selected for their immunogenicity, indicated by regression when transplanted into syngeneic mice. Tumor-specific and idiotype-specific immunity were measured in relation to age. Mice challenged with 1591 tumor cells produced anti-1591 lymphocytes, and were able to resist the tumors. Mice immunized against tumor-specific lymphocytes developed anti-idiotypic lymphocytes. Such mice were not resistant to tumors. Anti-idiotypic lymphocytes effective against anti-1591 lymphocytes had no effect on anti-1316 lymphocytes, indicating specificity. Animals at 6 mo of age showed reduced anti-idiotypic response when compared to 3-mo-old mice. Mice immunized at 9 or 12 mo did not develop anti-idiotypic response. When immunized against 1591, these older animals produced lymphocytes with considerable cross-reactivity with 1316 tumor cells. The data indicated that response to tumors in vitro remained constant with increasing age, but that cross-reactivity increased. Tumor-specific immunity in mice decreased with increasing age. Apparently tumor-specific T cells provide protection in young mice, but their dominance was lost in middle age. (28 Refs)

109. SPECIFICITY OF A MONOCLONAL ANTI-K 562 ANTIBODY.

Schienle HW, Muller-Ruchholtz W
Dept. Immunology, Univ. Kiel, Brunswiker Strasse 2-6, D-2300 Kiel, W. Germany
J Cancer Res Clin Oncol; 101(1):109-110 1981

Clone cells secreting an IgG antibody were obtained by immunizing female BALB/c mice with normal bone marrow cells and then hybridizing the mouse spleen cells with myeloma cells. The monoclonal antibody reacted preferentially with the K 562 cell line established from the pleural exudate of a patient in chronic myelocytic leukemia blast crisis. Weekly positive reactions were seen with a B-cell line (Daudi) and a monocyte cell line (U 937). The antibody, therefore, appears to define an antigen present on pluripotent stem cells in a high concentration and on slightly more differentiated precursor cells in a low concentration. (7 Refs)

CMI METHODOLOGY

110. ROLE OF T-CELLS IN THE MECHANISM OF REACTIVITY OF THE MICROPLATE LEUKOCYTE ADHERENCE INHIBITION ASSAY.

Raina S, Russo AJ, Jenkins D, Goldrosen MH
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Cancer Res; 41(10):3950-3955 1981

To characterize the role of mononuclear cells in the microplate leukocyte adherence inhibition assay, enriched populations of T-cells, B-cells, macrophages, and a nylon wool-adherent fraction consisting of B-cells and macrophages were prepared by a two-stage adherence procedure from spleen cells of normal C57BL/6J mice and mice bearing progressively growing murine colon adenocarcinoma 38 (MCA-38) tumors. These studies indicate that the reactive cell undergoing specific antigen-induced adherence inhibition was present in the macrophage fraction. This cell was programmed to undergo specific antigen-induced adherence inhibition by an MCA-38-sensitized B-cell. An enriched population of MCA-38 reactive cells. Pretreatment of the MCA-38-sensitized T-cell fraction with anti-Thy 1:2 serum and complement but not anti-Ig and complement or carbonyl iron to selectively deplete macrophages abolished the regulatory effect of the MCA-38-sensitized T-cell fraction. MCA-38-sensitized T-cells could prevent MCA-38-sensitized B-cells from programming normal macrophages in vitro but could not abolish the leukocyte adherence inhibition response of presensitized macrophages. Temporal studies of suppressor T-cell activity were performed throughout different phases of progressive tumor growth. Suppressor T-cells could be detected as early as 4 days post-MCA-38 tumor cell inoculation and persisted throughout MCA-38 progressive tumor growth. Titration studies of suppressor T-cells revealed the need for 4x the number of MCA-38-sensitized T-cells from small tumor bearers (day 4) in comparison to large tumor bearers (day 20) to achieve the same degree of suppression. Thus, in the MCA-38 system, sensitized T-cells exert a negative regulatory influence by preventing B-cell programming of normal macrophages. This negative regulatory influence increased in magnitude with the progressive growth of the MCA-38 tumor. (Author abstract) (25 Refs)

SUPPRESSOR CELL ACTIVITY

111. SUPPRESSOR CELL ACTIVITY IN A PROLIFERATIVE DISORDER OF T LYMPHOCYTES.

Kupa A, Thomas ME, Moore H, Bradley J, Zola H, Hooper M, Harding P

Dept. Clinical Immunology, Flinders Medical Centre, Bedford Park, S.A. 5000, Australia

Aust J Exp Biol Med Sci; 59(part3):263-275 1981

We report details of the immunological profile of a patient with the candidiasis endocrinopathy syndrome who has developed T-type chronic lymphocytic leukemia. The patient is anergic to a panel of delayed hypersensitivity skin tests, and has poor in vitro mitogenic responses, but B cell function in vivo is not impaired. Subsequent functional studies have revealed that cells from the patient have a significant suppressive effect in coculture (p less than 0.05) on the responses of healthy donor lymphocytes (NR) to the mitogen phytohemagglutinin (PHA). A degree of selectivity for the suppressive effect is suggested by the lack of similar effects on coculture responses to the mitogens concanavalin A (Con A) and pokeweed mitogen (PWM). Mitomycin C treatment of the patient's cells reduced their suppressive activity but significant suppression was still observed in the majority of PHA cocultures. The suppressor activity required the presence of the patient's cells in cocultures, as no suppression was observed when the patient's serum or cell culture supernatant were included instead of the patient's cells in NR cultures. (Author abstract) (21 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Akimaru K 54
Akimaru K 77
Akiyoshi T 29
Akopian RG 11
Aleksander SK 82
Ando K 53
Antonelli P 9
Arai H 52
Arnaud D 84
Ashby J 49
Ashikari H 9
Atkinson K 18
Attallah AM 83
Azuma I 59
Bandiera DC 19
Baral E 32
Bartlett SP 81
Bartocci A 87
Bazin H 93
Bennet M 81
Bersch N 79
Biberfeld P 88
Bier J 6
Blomgren H 32
Bockman RS 7
Boltz-Nitulescu 93
Bonmassar E 87
Bosslet K 55
Bradley J 111
Braun DW 9
Brodzki M 26
Brynes RK 50
Bunn PA 12
Burgio VL 22
Burton RC 81
Busbee DL 20
Cacciola E 8
Calkins CE 107
Calvis LA 19
Cantrell ET 20
Cassileth PA 3
Ciesluk S 46
Cirrincione C 7
Cline MJ 71
Cole DA 64
Collins KH 89
Coombs RR 49
Cooper RA 3
Cornelius J 94
Courcoul MA 84
Cunningham-Rund 7
Cunningham-Rund 9
Davis TW 99
Day NK 7
De Amorim AR 19
De Lapeyriere O 84
Deeg HJ 18
Demchenko TA 96
Den Otter W 97
Di Saia PJ 43
Doherty PC 56
Doney KC 4
Dosimov ZhB 48
Dullens HF 97
Dupont B 10
Dye ES 45
Dye ES 65
Dzhaginiian AI 96
Ebina T 38
Ebina T 70
Economou JS 28
Eremeev VS 48
Eremin O 49
Escaleira N 19
Faintuch J 24
Fernandes G 7
Fidler IJ 99
Filippa DA 9
Finogenova NA 47
Fisher RI 106
Flood PM 108
Folks T 83
Ford RJ 92
Fossieck B 12
Fukuhara S 42
Fukumoto Y 53
Fukuta T 2
Gallo RC 12
Gangadhar Rao M 5
Garaci E 87
Garofalo JA 7
Gentil F 19
Gilbert CJ 85
Gioia L 87
Giustolisi R 8
Gojobori M 13
Golde DW 71
Golde DW 79
Goldrosen MH 110
Good RA 10
Good RA 7
Good RA 90
Gorodilova VV 11
Grant CK 56
Groopman JE 79
Guglielmo P 8
Gupta S 7
Gusdon JP 43
Gustafsson A 72
Hanna MG 60
Hansen B 68
Harding P 111
Hargreaves HK 50
Haskill JS 100
Haskovcova H 27
Hattori T 1
Hattori T 42
Hawkins HK 50
Heacock EH 89
Heise ER 43
Hellstrom I 61
Hellstrom KE 61
Herbst GA 43
Hill JM 68
Hill NO 68
Hirao F 59
Hirose T 34
Hoffman-Lieberm 30
Hofstadter F 21
Holden HT 105
Homesley HD 43
Hooper M 111
Hopper KE 95
Hoshi K 39
Hunsmann G 86
Hutt-Fletcher L 85
Ikeda M 34
Ikehara S 90
Incefy GS 7
Ingenito GG 107
Inoue T 59
International A 33
International C 25
Irimajiri N 63
Ishida N 70
Ishigami H 36
Ishii J 2
Ishii T 39
Iwai S 2
Jakse G 21
Jeannin JF 91
Jenkins D 110
Jewell WR 66
Jezzi T 87
Jimi S 13
Kabelitz D 23
Kadin ME 44
Kalyanaraman VS 12
Kanetake H 34
Kapoor N 10
Karpowicz M 26
Karpowicz M 46
Kasahara T 38
Kato I 51
Kato T 78
Kauh YC 41
Kawaguchi M 29
Kawakubo Y 52
Kersey JH 76
Kesari G 5
Khan A 68
Kim T 76
Kim TH 50
Kirkpatrick D 10
Klareskog L 23
Klein E 88
Klein G 67
Klein G 88
Koba F 29
Kobayashi S 51
Kochergina NI 58
Kodama K 74
Kodama T 53
Koi M 70
Komiyama K 52
Kondo A 34
Konopka L 26
Konopka L 46

Kosova IP 58
Koyanagi N 52
Kripke ML 108
Krishnamachary 5
Krishnan EC 66
Krishnan L 66
Kumar V 81
Kupa A 111
Kurashige S 74
Kusaba Y 34
Lamon EW 80
Levitt SH 76
Liashenko VA 82
Liebermann D 30
Loeb E 68
Lotem J 103
Lovelace JV 43
Loveless SE 101
Lui VK 50
Lum L 18
Lundgren E 72
Luscombe HA 41
Lust JA 81
Maccario R 22
Maizel AL 92
Mannick JA 89
Mark R 21
Martin F 91
Martin RR 20
Mashiba H 13
Maslanka K 46
Matsumoto S 17
Matsumura K 69
Matsunaga K 13
Matsuo E 34
Matsuo Y 34
Matthews N 14
McLemore TL 20
Mercola KE 71
Migliorati G 87
Mills CD 45
Mills CD 65
Minagawa T 78
Minna JD 12
Mitsuhashi S 74
Miyake M 37
Miyata M 38
Miyazaki M 53
Miyazaki S 29
Mochizuki T 62
Moore H 111
Morioka Y 38
Morisue S 34
Mule JJ 61
Muller-Ruchholt 109
Munson AE 101
Muranyi-Kovacs 84
Muss HB 43
Mutai M 51
Nakamura H 73
Nakanashi K 1
Nakano A 1
Nakayama M 17
Nasretdinov TK 11
Nathan I 79
Nelson DS 95
Nelson M 95
Nicklisch U 6
Niimoto M 1
Nishiyama Y 52
Noma T 39
Normann SJ 94
North RJ 45
North RJ 65
O'Reilly RJ 10
Ogura T 59
Ohkawa M 17
Ohtsuka Y 40
Okita K 53
Olsson NO 91
Oshimi K 38
Pardue AS 68
Parker JW 31
Patarroyo M 88
Pawelski S 46
Pawleski S 26
Pekarek J 27
Peters LC 60
Petrini B 32
Pinsky CM 7
Pogosov VS 11
Poiesz BJ 12
Pollack MS 10
Posner LE 12
Quan SG 79
Ragab AH 50
Raina S 110
Ramshaw IA 56
Raz A 99
Re R 22
Reddy CR 5
Reisner Y 10
Rhee JG 76
Richards F 43
Rinaldi C 87
Rizzo M 8
Robert-Guroff M 12
Rumiantsev AG 48
Ruppert B 92
Ruscetti FW 12
Ruschak PJ 41
Russo AJ 110
Sachs L 103
Sachs L 30
Saito M 38
Saito M 70
Saito Y 34
Sakai Y 2
Santos IO 19
Saporoschetz I 89
Sawai K 35
Schardt M 94
Scheynius A 23
Schienle HW 109
Schirrmacher V 55
Schneider J 86
Schreiber H 108
Schulof RS 7
Schulz A 86
Seaman WE 57
Seigler HF 54
Seigler HF 77
Shapiro IM 67
Shapovalova SP 82
Shimbo T 40
Shindo K 34
Shiozawa I 2
Skorobogatova O 47
Skorobogatova O 48
Song CW 76
Sordillo FM 90
Sorkin E 94
Spiegelberg HL 93
Spurr CL 43
Stanton TH 61
Steele G 89
Stevens RH 64
Storb R 18
Storb R 4
Strejcek J 27
Strender LE 32
Stuhlmiller GM 54
Stuhlmiller GM 77
Suholet D 3
Sullivan K 18
Sylwestrowicz T 46
Takagi A 104
Takahashi K 38
Takahashi K 40
Takatsuki K 42
Takayama H 104
Takeda T 17
Takemoto T 53
Talal N 57
Tanaka Y 15
Tanaka Y 16
Tani T 1
Tanigawa T 104
Taramelli D 105
Thaler HT 7
Thomas ED 4
Thomas ME 111
Tjernlund UM 23
Toge T 1
Tono-oka T 17
Torhorst J 98
Trotta PP 90
Tsoi MS 18
Tsubota W 53
Tsuji H 29
Tsukahara Y 2
Uchino H 42
Uchiyama T 42
Ueshima Y 42
Ugazio AG 22
Umezawa I 52
Urban JL 108
Urritia-Shaw A 83
Vanhaelen CP 106
Varella AD 19
Varesio L 105
Volsky B 67
Volsky DJ 67
Votava V 27
Wakasugi H 38
Walia AS 80
Wang BS 89
Warren HS 75
Wasserman J 32
Weiden PL 4
Wilson RG 102
Witherspoon RP 18
Woodard J 50

Wray NP 20
Yamada Y 1
Yamakura T 40
Yamamura Y 59
Yamashita U 73
Yanagawa E 1
Yata J 39
Yeatman TJ 83
Yokokura T 51
Yoshida T 74
Yoshimoto T 59
Zinkernagel RM 56
Zola H 111
Zywicka-Lopaciu 46

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IMMUNOBIOLOGY AND CANCER
Functional Aspects of Cellular Immunity

SERIES CB15 No. 82/02

FEBRUARY, 1982

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In this issue:

- **EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS** 1-60
- **EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS** 61-74
- **EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION** 75-90
- **THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE** 91-98
- **ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY** 99
- **RELATED BIOLOGY OF IMMUNE CELLS** 100-101
- **CMI METHODOLOGY** 102-108
- **SUPPRESSOR CELL ACTIVITY** 109
- **OTHER RELATED STUDIES** 110-114

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. EFFECT OF EXOGENOUS METHIONINE DEPLETION ON PROTEIN SYNTHESIS IN NORMAL AND LEUKEMIC LEUKOCYTES CULTURED IN VITRO.

Tautt J, Maj S, Chlopkiewicz B, Koziorowska J
Zaklad Lekow Witaminowych, Instytut Lekow, ul. Chelmska 30/34, 00-725 Warsaw, Poland
Acta Haematol Pol; 12(2):69-75 1981

The effect on protein synthesis of methionine deprivation or of its replacement by homocysteine in the culture medium was studied in peripheral blood lymphocytes and leukocytes from 8 healthy donors and 17 adult patients with acute leukemia (10 with acute myeloblastic leukemia and 7 with acute lymphoblastic leukemia). The effect was evaluated by labeling experiments with tritiated valine. Protein synthesis by lymphocytes and leukocytes of healthy donors was significantly inhibited in the absence of methionine, but there was no significant difference in inhibition between methionine-free cultures and those cultures in which methionine was replaced by homocysteine. Similar findings were obtained for the leukemic leukocytes as well in the 34-hr culture. Here, the protein synthesis was inhibited by 0% in 4/17 cases, and by 15-50% in 13/17 in the absence of methionine; by 0% in the same 4 cases, and by 18-57% in the presence of homocysteine. (12 Refs) (In POL)

2. NEW DATA ON CHRONIC LYMPHOCYTIC LEUKEMIA.

Rupniewska ZM, Dmoszynska-Giannopoulou A
Klinika Hematologii, Instytut Chorob Wewnecrznych Akademii Medycznej, ul. Jaczewskiego 8, 20-950 Lublin, Poland
Acta Haematol Pöl; 12(2):107-112 1981

Recent studies on chronic lymphocytic leukemia (CLL) are reviewed. More than 75% of the patients are over 60 yr old, and CLL affects twice as many men as women. The serum immunoglobulin is often polyclonal, and ther is hypogammaglobulinemia in the majority of the cases. The leukemia cells carry Fc IgG receptor, receptor for complement (RC), and receptor for mouse erythrocytes. About 11% of all cases are characterized by the presence of two subtypes of complement receptor (1 RC and 2 RC). T-cell markers occur in 1-2.9% of all cases. (59 Refs) (In POL)

3. CHARACTERISTIC FEATURES OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN WITH 0-CELLS IN THE BONE MARROW AND PREDOMINANCE OF T- OR B-CELLS IN THE PERIPHERAL BLOOD.

Lenskaia RV, Samochatova EV, Rumiantsev AG, Izotova TA
No affiliation given
Probl Gematol Pereliv Krovi; 26(7):20-24 1981

Different markers of the leukemic cells in the bone marrow and the peripheral blood were reported in 11 children (5 boys, 6 girls, aged 4 to 13 yr) with acute lymphoblastic leukemia (ALL). Examination of the bone marrow showed total metaplasia with lymphoid leukemic cells; greater than 80% of leukemic cells could be identified as null-lymphocytes. Analysis of the lymphoid cells in the peripheral blood showed predominance of T-lymphocytes in 10 patients and predominance of B-lymphocytes in 1. Chemotherapy (prednisone in combination with vincristine) induced stable and prolonged remission in 10/11 patients. (8 Refs) (In RUS)

4. IMMUNOLOGICAL REACTIVITY OF PATIENTS WITH MALIGNANT TUMORS OF THE HEAD AND NECK. PART 4. IMMUNOLOGICAL CHANGES ACCOMPANYING SURGERY AND RADIOTHERAPY.

Sakaguchi K, Okuda M, Tomiyama S
Dept. Otolaryngology, Nippon Medical Sch., Tokyo, Japan
Nippon Jibiinkoka Gakkai Kaiho; 84(2):129-138 1981

Humoral and cellular immunities were examined before and after curative surgery or 60Co radiotherapy in 95 patients with various malignant tumors of the head and neck. The tumors occurred in the nasal sinuses and cavity in 19 patients, tongue or oral cavity in 11, pharyngoesophageal region in 18, larynx in 20, thyroid in 12, and other regions in 15. The radiotherapy consisted of 200-rad fractions administered 5x/wk for a total of 4,000-6,000 rads. Parameters of humoral factors such as total serum protein, serum protein distribution, levels of immunoglobulins, carcinoembryonic antigen (CEA), serum complement (CH50), and parameters of cellular factors such as peripheral lymphocyte count, phytohemagglutinin (PHA) skin test, and lymphocyte blastogenic response to PHA were measured several days before surgery and radiotherapy and after sufficient postoperative and postirradiation recovery time. Despite apparent similarities in the process of tumor disappearance, changes in immunological parameters were observed with respect to the treatment modality. In the patients who were treated with surgery, humoral immunity (levels of serum alpha2-globulin, CH50, IgA, IgG, and CEA) was elevated, but cellular immunity showed no changes. On the other hand, in the patients treated with radiotherapy, humoral immunity was not changed, but cellular immunities were significantly depressed (ie decreased peripheral lymphocyte counts and blastogenic response to PHA). Recovery of pretreatment immunity was observed a few mo postoperatively in the surgical patients, but suppressed immunity in the radiotherapy patients was thought to persist for a more prolonged period. (22 Refs) (In JPN)

5. IMBALANCE OF T-CELL SUBPOPULATIONS DOES NOT RESULT IN DEFECTIVE HELPER FUNCTION IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Inoshita T, Whiteside TL
(c/o Whiteside) Dept. Pathology, Univ. Pittsburgh, Sch. Medicine, 406 Scaife Hall, Pittsburgh, PA, 15261
Cancer; 48(8):1754-1760 1981

The T-lymphocyte subpopulations identified by the Fc receptors for IgG (TG cells) and IgM (TM cells) in 12 patients with B-cell chronic lymphocytic leukemia (CLL) were quantitated and studied for functional capabilities in an in vitro assay. The TG cells in patients were elevated in relation to age- and sex-matched normal controls (p less than 0.05) resulting in an altered TM/TG ratio of 1.8 +-0.76 in CLL versus 5.9 +-3.7 in controls (mean +- SD, p less than 0.001). Despite this altered TM/TG ratio, the functional capability of the CLL T cells to regulate the terminal differentiation of B cells was found to be normal as reflected by the mean helper-suppressor score of 0.77 +-0.13 (+- SEM) obtained for both patients and controls. This unimpaired capacity of the T cells from CLL patients to help normal B cells mature into Ig-secreting cells indicated that hypogammaglobulinemia and monoclonal serum Ig in these patients m ay be a result of either an intrinsic defect in the B lymphocytes or their replacement by a neoplastic clone rather than a defect in the immunoregulatory T cells. (Author abstract) (39 Refs)

6. SERUM IGD IN HODGKIN'S DISEASE.

Gobbi PG, Merlini G, Lattanzio G, Perugini S

Istituto di Patologia Medica Ia, Universita di Pavia, Policlinico San Matteo, 27100 Pavia, Italy

Haematologica (Pavia); 66(1):35-45 1981

Serum IgD levels were measured in 56 Hodgkin's disease (HD) patients (34 male, 22 female; 13-63 yr old). Mean value of serum IgD was significantly higher in HD patients than in normal subjects. In HD patients with lymphocyte predominance, the IgD levels appeared normal and were significantly lower than in patients with the other three histological types of HD. Among the latter, only nodular sclerosis and mixed cellularity groups exhibited IgD levels significantly higher than normal; the difference in lymphocyte depletion subjects was not significant. In patients with stages other than Stage I HD, IgD levels were significantly higher than normal; no significant difference was observed between these different stages. No significant relationship was found between IgD level and sex, spleen involvement or splenectomy, or form and length of treatment. A fair correlation was observed between serum IgD level and therapeutic response: IgD decreased significantly with remission but not with partial or non-response. Serum IgD may reflect the immune reaction to tumor-associated antigens of the Hodgkin-Sternberg cells, and be of value in monitoring response to treatment. (18 Refs)

7. HUMAN LARGE GRANULAR LYMPHOCYTES: SPONTANEOUS AND INTERFERON-BOOSTED NK ACTIVITY AGAINST ADHERENT AND NONADHERENT TUMOR CELL LINES.

de Landazuri MO, Lopez-Botet M, Timonen T, Ortaldo JR, Herberman RB

Dept. Immunology, Clinica Puerta de Hierro Universidad Autonoma, Madrid, Spain

J Immunol; 127(4):1380-1383 1981

Human natural killer (NK) cells against K-562 tumor cells have been morphologically identified as large granular lymphocytes (LGL). We have investigated whether LGL are also responsible for NK activity against a variety of adherent and nonadherent tumor cell lines. LGL-enriched fractions, obtained by centrifugation of nonadherent mononuclear cells on discontinuous density gradients of Percoll, contained high levels of spontaneous and interferon-(IFN) boosted NK activity against each the target cells tested. In contrast, the LGL-depleted fractions, which contain most of the typical small lymphocytes, were devoid of NK activity and did not develop appreciable activity after treatment with IFN. The ability of the different fractions to exert NK activity correlated with their capacity to form conjugates with nonadherent tumor cells. Reconstitution of the different fractions with macrophages did not increase the NK activity of already cytotoxic fractions and did not induce appreciable activity in the LGL-depleted fractions. On the other hand, mixtures of highly cytotoxic and nonreactive cell fractions did not reveal the presence of suppressor cells for NK in the nonreactive fractions. Taken together, our data demonstrate that both spontaneous and IFN-boosted NK activity is confined to the LGL-enriched fractions and suggest that LGL are the main effector cells exerting NK cytotoxicity against a variety of adherent as well as nonadherent tumor cell lines. (Author abstract) (17 Refs)

8. AN OVERVIEW OF IMMUNOTHERAPY, ESPECIALLY OF BREAST CANCER.

Gottlieb AA

Dept. Microbiology and Immunology, Sch. Medicine, Tulane Univ., New Orleans, LA, 70112

Comment Res Breast Dis; 2:103-132 1981

Immunotherapy, particularly as applied to treatment of breast cancer, is reviewed. Parameters of immune responsiveness to breast cancer, such as lymphocyte transformation and infiltration, response to skin test antigens, and peripheral lymphocyte counts, are described. The nature of viral antigens in breast cancer is discussed. Suppressors and suppressor cells, including non-T cell suppressor cells, are discussed. Active, adoptive, and passive immunotherapies are detailed, including use of Corynebacterium parvum, BCG, levamisole, immune RNA, interferon, glucan, and transfer factor. Future research into the isolation of those components of biological agents, such as BCG and C parvum, which produce particular effects on immune response, is urged. (127 Refs)

9. HODGKIN'S DISEASE: ANALYSIS OF FIFTY-THREE AUTOPSY CASES.

Aozasa K, Ito H, Bandai H, Yamamoto S

Dept. Pathology, Osaka Univ., Nakanoshima 4-chome 3-57, Kita-Ku, Osaka, 530, Japan

Acta Pathol Jpn; 31(4):663-673 1981

Eighty-eight autopsy cases originally diagnosed as Hodgkin's disease (HD) were reevaluated, and 53 cases were obtained as HD. Fifty three cases with HD were composed of 46 males and 7 females and 52 cases had an active disease. Frequencies of four subtypes such as lymphocytic predominant, mixed cellularity, lymphocytic depletion, and nodular sclerosis were found to be 25, 54, 14, and 7%, respectively at biopsy and 12, 38, 44, and 6%, respectively at autopsy, showing transition of subtype in HD. The manner of organ involvement, deviation of histologic figures between nodes and/or other organs, associated diseases including non-bacterial inflammation of lung, amyloidosis and secondary malignancy and differential diagnosis of HD from the confusing diseases observed in our series were described. (Author abstract) (44 Refs)

10. AN INTRODUCTION TO THE MODERN HISTOLOGICAL CLASSIFICATION OF THE NON-HODGKIN'S LYMPHOMAS.

Musso LA

231 Macquarie St., Sydney, New South Wales 2000, Australia

Australas J Dermatol; 22(1):24-27 1981

The histological classification of non-Hodgkin's lymphomas based on the existence of T and B cell lymphocytes, lymphocyte transformation, and appearance of the follicular cell center (FCC) of the lymph gland is described. Most of the information presented is based on Lukes immunological classification schema. B and T immunoblasts are described. B immunoblasts are cells which resemble large non-cleaved FCC, but with more deeply staining amphophilic and pyroninophilic cytoplasm. The T immunoblasts have pale water-clear cytoplasm with well-defined interlocking plasma membranes giving a cohesive appearance. Histological classifications described include U cell (undefined) lymphoma, small lymphocytic T-cell lymphoma, immunoblastic T-cell sarcoma, histiocytic type neoplasms, small B-cell lymphoma, small and large cleaved and uncleaved FCC lymphomas, and immunoblastic B-cell sarcoma. (2 Refs)

11. INFECTION IN THE COMPROMISED HOST.

Young LS
Univ. California, Los Angeles, CA
Hosp Pract; 16(9):73-84 1981

Impairment of host resistance, development of infection, diagnosis, therapy, and prevention are reviewed. Impairment of host resistance is due to a reduced number of functional phagocytes, diminished cell-mediated immunity, faulty antibody production, or damage to mechanical barriers to infection. These factors may be due to disease itself or to treatments. Acute leukemia involves functional leukopenia, deficient leukocyte mobilization, and defective phagocytosis. In Hodgkin's disease cell-mediated immunity is impaired. In multiple myeloma, chronic lymphocytic leukemia, or histiocytic lymphoma antibody production is impaired. Treatments which reduce immune response include immunosuppressive drugs aimed at abnormal bone marrow, corticosteroids, and high-dose dexamethasone. Some neoplastic diseases are associated more with certain types of infection than with others. Infections may be due to endogenous or exogenous pathogens. Transmission may be by a number of paths, including hand carriage by hospital personnel, contaminated invasive devices, or infusion fluids. Two portals of entry for opportunistic infections are the oropharynx and the lower digestive tract. Aggressive therapy, using agents such as trimethoprim-sulfamethoxazole or penicillin, is indicated. Prophylactic measures include varying degrees of patient isolation and administration of drugs. (no Refs)

12. ACID PHOSPHATASE ACTIVITY OF THE LYMPHOCYTES DURING POLYCHEMOTHERAPY OF LYMPHOPROLIFERATIVE DISEASES.

Rudzka E, Holowiecki J, Japa J, Krawczyck M, Jarczok K, Stella-Holowiecka B
I Clinic Internal Medicine, Inst. Internal Medicine, Silesian Medical Acad., Reymonta 8, 40-029 Katowice, Poland
Arch Immunol Ther Exp (Warsz); 29(2):133-139 1981

Lymphocyte acid phosphatase (AP) activity was measured before and during combination chemotherapy in seven patients (age 16-72 yr) with acute lymphoblastic leukemia (ALL: 3 cases) or malignant lymphoma (4 cases). A marked and lasting reduction of AP-positive lymphocytes occurred in null cell ALL after L-asparaginase administration (LA), and it was associated with a change from a granular to a diffuse and dispersed reaction. In ALL patients in remission, vincristine (VR) and adriamycin depressed AP activity. Enzyme levels in the lymphoma patients declined immediately after the onset of COP treatment (cyclophosphamide, VR, and prednisone), but they normalized between cycles and after full remission was reached. Changes in AP expression after LA treatment could reflect the inability of leukemic cells to synthesize asparagine. (16 Refs)

13. THE RESPONSE OF CANCER PATIENTS' LYMPHOCYTES TO MITOGEN. THE EFFECT OF INDOMETHACIN ON ADHERENT AND NON-ADHERENT CELLS' ACTIVITY.

Pituch-Noworolska A
Dept. Microbiology and Clinical Immunology, Inst. Pediatrics, Wielicka 265, 30-663 Cracow, Poland
Arch Immunol Ther Exp (Warsz); 29(2):161-165 1981

Lymphocytes from 13 patients (age 28-83) with Stage III or IV breast, stomach, and colon cancer and lymphocytes from 13 normal subjects (age 28-42 yr) were tested for response to concanavalin A (Con A) in the presence or absence of indomethacin (ID). ID had no effect on the poor mitogen response of patient nonadherent cells (NAC) cultured with autologous adherent cells (AC). However, it caused a significant increase in the response of normal NAC cultured with autologous AC. Responses of normal NAC cultured with patient AC also increased in the presence of ID; this suggested that prostaglandins (PG) were not responsible for the depressed Con A response of patient lymphocytes and that patient AC were not defective in ability to produce PG. (16 Refs)

14. SCREENING SYSTEM FOR THE EVALUATION OF PREPARATIONS WITH POTENTIAL CYTOSTATIC AND IMMUNOTROPIC ACTIVITY. I. DERIVATIVES OF 4,5-DIHYDRO-2H-PYRIDAZINONE-3.

Gieldanowski J, Steuden W, Skowronska J, Goroczyca W, Doskocz W
Dept. Experimental Therapy, Inst. Immunology and Experimental Therapy, Polish Acad. Sciences, Czerska 12, 53-114 Wroclaw, Poland
Arch Immunol Ther Exp (Warsz); 29(2):249-256 1981

Nineteen 4,5-dihydro-2H-pyridazinone-3 derivatives with potential cytostatic and immunosuppressive activity were tested for their effects on blastic transformation in human lymphocytes stimulated with phytohemagglutinin. Two piperazine derivatives (PA-4 and PA-5) and a pyrrolidine derivative (PA-3) completely inhibited 14C-thymidine incorporation in lymphocyte nuclei at concentrations of 10(-3) to 10(-4) M. As a result of their marked antimitotic activity, these compounds are probably cytostatic and immunosuppressive. (8 Refs)

15. SCREENING SYSTEM FOR THE EVALUATION OF PREPARATIONS WITH POTENTIAL CYTOSTATIC AN D IMMUNOTROPIC ACTIVITY. II. DERIVATIVES OF PROPIONIC AND HYDROXYBUTYRIC ACIDS AND OF TETRAHYDROFURANONE-2.

Gieldanowski J, Steuden W
Dept. Experimental Therapy, Inst. Immunology and Experimental Therapy, Polish Acad. Sciences, Czerska 12, 53-114 Wroclaw, Poland
Arch Immunol Ther Exp (Warsz); 29(2):257-265 1981

Propionic acid (PA), hydroxybutyric acid (HA), and tetrahydrofuranone-2 (TH) derivatives were tested for their effects on the blastic transformation of phytohemagglutinin-stimulated human lymphocytes. Of 28 compounds evaluated, PA derivatives and methylpropionic acid derivatives (except linear compounds) strongly inhibited 14C-thymidine incorporation in nuclei of stimulated lymphocytes. HA derivatives were weakly active, and TH derivatives inhibited lymphocyte transformation only at high concentrations. No compound was as inhibitory as mitomycin C. The lymphocyte transformation assay can be used to screen new compounds for their antimitotic, cytostatic, and immunosuppressive activity. (7 Refs)

16. LEUKOCYTE MIGRATION INHIBITORY FACTOR (LMIF) RELEASE BY HUMAN COLONIC LYMPHOCYTES.

Bartnik W, ReMine SG, Shorter RG
Dept. Gastroenterology and Metabolism, Medical Center Postgraduate Education, Goszczynskiego 1, 02-616 Warsaw, Poland
Arch Immunol Ther Exp (Warsz); 29(3):397-405 1981

Peripheral blood lymphocytes (PBL) and colonic mucosa lymphocytes (CML) from 8 patients with ulcerative colitis, 10 with colorectal carcinoma, and 4 with other colonic diseases were tested for their ability to release leukocyte migration inhibitory factor (LMIF) upon stimulation by concanavalin A

(Con A) or the Kunin common enterobacterial antigen. PBL and macrophage-depleted CML from patients and healthy controls released LMIF following nonspecific stimulation with Con A. Although lymphocytes from ulcerative colitis patients were less active than those from carcinoma patients, the difference was not significant. Upon stimulation with Kunin antigen, PBL and CML from patients with active ulcerative colitis showed significantly greater LMIF activity than PBL and CML from patients with mild colitis or other large bowel diseases including Crohn's disease. The possibility that hypersensitivity to Kunin antigen plays a role in the pathogenesis of ulcerative colitis is discussed. (24 Refs)

17. LONG-TERM ABNORMALITIES IN T AND B LYMPHOCYTE FUNCTION IN CHILDREN FOLLOWING TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKAEMIA.

Layward L, Levinsky RJ, Butler M
(c/o Levinsky) Dept. Immunology, Inst. Child Health, 30 Guilford St., London, W.C.1, England

Br J Haematol; 49(2):251-258 1981

T and B lymphocyte function as assessed by pokeweed mitogen stimulation and concanavalin A suppression was studied in 40 children with acute lymphoblastic leukemia who were in remission and off all treatment. Both plasma cell and Ig production was reduced in off-treatment patients, particularly in those who had received cyclophosphamide as part of their treatment. The ability to suppress Ig production was also significantly reduced in these patients. These abnormalities were long-standing and were apparent up to 5 yr after stopping treatment with no indication of a return to normality. No clinical correlations have been observed. (Author abstract) (20 Refs)

18. HISTONE VARIANT COMPOSITION OF NORMAL AND LEUKAEMIC HUMAN LYMPHOCYTES: ANALYSIS BY GEL ELECTROPHORESIS OF WHOLE CELLS AND NUCLEI.

Froussard P, Tempelis LD, Levy SB
(c/o Levy) Div. Hematology-Oncology, Tufts-New England Medical Center, 136 Harrison Ave., Boston, MA, 02111

Br J Haematol; 49(2):275-282 1981

The histone variant composition of normal and leukemic lymphocytes was analyzed using a method which circumvented endogenous cellular proteolysis. Whole cells were solubilized in buffer containing protamine which released the histones from the DNA and allowed their immediate analysis by Triton X-100-acetic acid - urea gel electrophoresis. The results were comparable to those obtained with histones which had been acid-extracted from cells, nuclei or chromatin; however, the new method was more reproducible since proteolysis was controlled. By histone variant analysis, chronic lymphocytic leukemia patients could be separated into two groups. One group had lymphocytes with a histone H2a variant ratio of about 1.0; this finding resembled lymphocytes (75-85% T cells) from normal individuals. The larger group had lymphocytes with a reproducibly lower histone H2a variant ratio; these cells had a relative increase in the second variant, H2a.2. The two groups of patients could not be distinguished by clinical disease state. No other differences were noted in the histone variant composition of lymphocytes from normal and leukemic individuals. (Author abstract) (17 Refs)

19. THE MIGRATORY PROPERTIES OF INDIUM-111 OXINE LABELLED LYMPHOCYTES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA.

Wagstaff J, Gibson C, Thatcher N, Crowther D
Dept. Medical Oncology, Christie Hosp., Holt Radium Inst., Wilmslow Road, Manchester M20 9BX, England
Br J Haematol; 49(2):283-291 1981

These studies describe the application of a new method for following the migration of autologous lymphocytes in normal subjects and patients with chronic lymphocytic leukemia (CLL). There is evidence that Indium 111 oxine is a reliable radioactive cell label for in vivo studies of lymphocyte traffic in man. In normal subjects, where 60-70% of the lymphocytes labeled are T cells, the results are different from those of previous workers. The lymphocytes leave the blood initially but later return to it. It is believed that this is due to the reappearance of cells which at first entered the spleen. It is suggested that the difference between these data and those of Hersey (1971) is due to the failure of lymphocytes in the latter studies to return to the blood after primary migration. In CLL no such reappearance in the blood is seen and the lymphocytes do not leave the spleen in significant numbers over 48 hr. This suggests that CLL B cells either do not recirculate through spleen or that their transit time is greater than 48 hr. Bone marrow localization in CLL patients is greater than in the normal subjects, suggesting that either a larger proportion of the neoplastic B lymphocytes enter this compartment or their transit time through it is longer than the transit time of a normal T cell predominant population. Localization in normal-sized lymph nodes in patients with CLL is less than that in the lymph nodes of normal subjects. This may possibly be explained by the greater propensity of T lymphocytes to enter lymph nodes than B lymphocytes, or by the altered migratory properties of CLL B lymphocytes as compared with normal B cells. (Author abstract) (17 Refs)

20. DEPRESSION OF THE GENERATION OF CELL-MEDIATED CYTOTOXICITY BY MACROPHAGE-LIKE SUPPRESSOR CELLS IN BLADDER CARCINOMA PATIENTS.

Spina CA, Dorey F, Vescera C, Brosman S, Fahey JL
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Cancer Res; 41(11,part1):4324-4330 1981

Depressed T-lymphocyte function as assessed by delayed-type hypersensitivity reactions and in vitro proliferative response to mitogens is a characteristic finding in many types of solid tumors, including bladder carcinoma. Peripheral blood WBC from 16 patients with transitional cell carcinoma of the bladder were compared with age-matched, control subjects. Both the unfractionated WBC containing 10 to 30% monocytes and the lymphocyte-enriched preparations, obtained by monocyte depletion with iron filling ingestion, were analyzed. Mixed WBC culture-induced cytotoxicity was depressed in the patient group; the amount of depression was directly correlated to the extent of the disease. In patients who underwent surgical removal of tumor, the mixed WBC culture-induced cytotoxicity appeared normal. This mixed WBC culture-generated cytotoxic response was a more sensitive indicator of tumor effect than was the induced proliferative response. Removal of phagocytic or adherent monocytes from the responding cell population caused a significant increase in the generated cytotoxicity, especially in those patients with invasive disease. These suppressive effects could be partially reconstituted by quantitative addition of the separated monocytes back to the responding lymphocyte culture. The depressed lymphocyte-mediated cytotoxicity present in these bladder cancer patients was due, in a major part, to a circulating macrophage-like cell with active suppressor function. (Author abstract) (39 Refs)

21. INDUCTION BY TUMOR-PROMOTING PHORBOL DIESTER OF COLONY-STIMULATING ACTIVITY IN HUMAN MYELOID LEUKEMIA CELLS TRANSFORMED TO MACROPHAGE-MIMICKING CELLS.

Svet-Moldavskaya IA, Arlin Z, Svet-Moldavsky GJ, Clarkson BD, Koziner B, Mendelsohn N, Zinzar SN, Holland JF
Dept. Neoplastic Diseases, Mount Sinai Sch. Medicine, New York, NY, 10029
Cancer Res; 41(11,part1):4335-4340 1981

The tumor-promoting phorbol diester, 12-O-tetradecanoylphorbol-13-acetate (TPA), appears to induce a macrophage-mimicking transformation of cells in human promyelocytic leukemia continuous cultured line HL-60, cells from normal human and chronic myeloid leukemia bone marrow, and cells from human acute leukemias. In the present experiments, peripheral blood and/or bone marrow nucleated cells from 12 patients with acute myeloblastic leukemia (AML), 1 with acute promyelocytic leukemia (APL), 1 with acute myelomonocytic leukemia, 3 with myeloid blastic crisis of chronic myelogenous leukemia (BI-CML), and 2 with acute lymphocytic leukemia (ALL) were exposed to TPA at concentrations from 10(-7) to 10(-9) M. After 1 to 4 days, in all cases except ALL, the cells acquired the peculiar morphology of macrophage-mimicking cells with multiple long or short thin pseudopods. We studied the ability of leukemia promyelocytes from HL-60 cells and cells from AML, APL, and BI-CML to produce colony-stimulating activity (CSA) after treatment with TPA. The data showed that CSA production occurs in leukemic blasts treated with TPA themselves but not by some cellular minority present in leukemic blood and bone marrow buffy coats and possibly activated by TPA. TPA (10(-8) M) itself incubated in culture medium without any cells up to 7 days did not possess any CSA. These experiments show that TPA is able not only to transform leukemic myeloid cells to macrophage-mimicking cells but also to induce CSA production by these cells. (50 Refs)

22. LYSIS OF FRESH AND CULTURED AUTOLOGOUS TUMOR BY HUMAN LYMPHOCYTES CULTURED IN T-CELL GROWTH FACTOR.

Lotze MT, Grimm EA, Mazumder A, Strausser JL, Rosenberg SA
Surgery Branch, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 41(11,part1):4420-4425 1981

Human lymphocytes derived from the peripheral blood of patients with a variety of cancers were grown in T-cell growth factor (TCGF) and tested in a 4-hr 51Cr microcytotoxicity assay against fresh and cultured autologous tumor, autologous cultured skin fibroblasts, and autologous fresh peripheral blood lymphocytes. Lymphocytes grown in TCGF caused significant lysis of autologous cultured tumor and fibroblasts but caused little lysis of fresh autologous peripheral blood lymphocytes in all of seven patients tested. This lytic activity against autologous cultured cells was not dependent on the source of serum used in culturing the lymphoid cells or the targets. Lymphoid cells grown in TCGF also were capable of causing selective lysis of fresh autologous tumor cells that had never been in culture in five of nine patients. Lymphoid cells growing in lectin-free TCGF caused selective lysis of autologous tumor in five of seven patients. These observations demonstrate that peripheral lymphoid cells grown in TCGF can be lytic for autologous cultured and autologous fresh tumor compared to the lysis of fresh autologous peripheral blood lymphocytes. The fact that these autoreactive cells, lytic for tumor, may be expanded to large numbers in TCGF suggests a possible role for these cells in studies of the control of the cytotoxic response of activated cells to tumor and possibly in the immunotherapy of tumors as well. (Author abstract) (37 Refs)

23. A CLINICAL PERSPECTIVE ON CELL MARKERS IN ACUTE LYMPHOCYTIC LEUKEMIA.

Bowman WP, Melvin SL, Aur RJ, Mauer AM
Div. Hematology-Oncology, St. Jude Children's Res. Hosp., Memphis, TN, 38101
Cancer Res; 41(11,part2):4794-4801 1981

Two hundred consecutive new patients, with acute lymphocytic leukemia (ALL) have been studied with a battery of five cell marker assays to determine if a classification system with prognostic significance can be developed; 182 have been classified among four groups as follows: 33 T-cell, 3 B-cell, 126 common, and 20 undifferentiated ALLs. Patients with T-cell disease are likely to have unfavorable clinical prognostic features and a poor response to therapy. Rare patients with B-cell disease are closely related clinically to non-Hodgkin's lymphoma. Those with common ALL infrequently have unfavorable clinical features and have a superior outcome to that of T-cell patients. Children with undifferentiated markers seem to respond less well to treatment than do those with common ALL, yet may not be identifiable as poor risk by clinical features. What remains to be resolved with further observation is whether these marker patterns are more reliable indicators of prognosis than the usual clinical determinants predisposing to treatment failure (high WBC count, mediastinal mass, and CNS disease). At the present time, it appears that in the absence of poor-risk clinical prognostic features, patients with common ALL are more likely to have lasting remissions than those with RBC-rosette-positive T-cell disease or those with ALL that is undifferentiated by markers. (Author abstract) (9 Refs)

24. HISTOPATHOLOGY OF LARGE CELL LYMPHOMAS (REPORT NO 9).

Henry K
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Clin Radiol; 32(5):505-512 1981

The purpose of this communication is to discuss and illustrate the different microscopical features of members of this important group of large cell lymphomas and to give some indication of prognosis in relation to histopathology. The diffuse large cell lymphoma is a heterogeneous category of tumor previously designated reticulum cell sarcoma in traditional classifications, and 'histiocytic' by Rappaport. The majority are, however, large lymphoid cell tumors which on the basis of their light microscopic anatomy may be subdivided into those of follicle center (B-lymphocytic) origin, immunoblastic type of either B- or T-lymphocytic origin, and 'undifferentiated' - meaning that although acceptable as lymphoid in nature at light microscopical level there are no further distinguishing features. Plasma cell (extramedullary) lymphomas are separately categorized. A smaller but significant minority group are of histiocytic (mononuclear phagocytic) derivation. Rarely tumors are encountered involving peripheral lymphoreticular tissue but which are derived from other cell types indigenous to the lymphoreticular and mononuclear and phagocytic system. (Author abstract) (33 Refs)

25. MODULATION OF NATURAL CYTOTOXICITY BY ALLOANTIBODIES: PART II - EFFECT OF ANTI HLA ANTISERA ON THE NATURAL KILLER ACTIVITY OF HUMAN PERIPHERAL BLOOD LEUKOCYTES AGAINST A HUMAN AND A MURINE CELL LINE.

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Clinical Immunology Section, Gerontology Res. Center, NIA, NIH, Baltimore City Hospitals, Baltimore, MD, 21224
Indian J Exp Biol; 19(7):595-597 1981

The effects of specific anti HLA antisera on the natural killer (NK) activity of human peripheral blood lymphocytes (HPBL) were investigated. NK activity of HPBL against human leukemia cell line K562 and mouse cell line YAC was studied in a 4 hr 51Cr release assay; different concentrations of anti HLA antisera were included in the cytotoxicity incubation medium. Anti HLA-A1 and anti HLA-B17 antisera inhibited the lysis of YAC cells by HPBL in a dose-dependent manner; no significant effect on K562 cells was noted. No effect on lysis of either type of target cells was noted with anti HLA-A9 and HLA-B5 antisera. Anti HLA antisera exerted the effect either at the effector or target cell level or both. The levels of NK induced K562 lysis was much higher (45-95%) than the levels of YAC cell lysis (5-15%). When NK activity of control or anti HLA antiserum treated HPBL was studied at a range of effector:target (E:T) ratios against K562 and YAC targets, anti HLA antiserum treatment did not influence the NK activity of HPBL against K562 target cells, even at lower E:T ratios. Marked inhibitory effects of the same treatment on NK activity of HPBL against YAC targets was observed at all E:T ratios. (9 Refs)

26. IMMUNOLOGICAL STUDY ON HODGKIN'S DISEASE WITH SPECIAL REFERENCE TO LYMPHOCYTE INHIBITOR.

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J Formosan Med Assoc; 80(1):55-67 1981

The characteristic T-cell anergy of Hodgkin's disease (HD) was studied in 5 HD patients and compared with that observed in 8 patients with non-Hodgkin's lymphoma (NHL) and 28 healthy controls. The presence of a serum factor in HD patients which is capable of suppressing phytohemagglutinin (PHA) blastogenesis of T-cells from normal controls and HD patients was examined. Lymphocytopenia was found in 2/5 HD patients but not in NHL patients. The percentages of T and B lymphocytes were similar in all three groups. Positive reaction to id purified protein derivative of tuberculin test occurred in 1/5 HD patients, 3/8 NHL patients, and 11/16 controls. The PHA transformation index (TI) was markedly depressed in HD. Differences in PHA TI were not significant between HD and NHL patients, although the PHA TIs of both groups differed significantly from those of controls. Serum IgG, IgM, and IgA levels were within normal ranges for the HD patients. Data implied that some factor was present in the sera of HD patients which was capable of suppressing the transformation response of normal lymphocytes to PHA. The effect of this serum inhibitory factor on the TI of different lymphocyte sources was studied. The lymphocytes from the three groups were incubated in 20% fetal calf serum (FCS) and 20% HD serum (HS) from HD Cases A, C, and D, and the ratios of PHA TI in HS to PHA TI in FCS were measured. The ratios were much lower in HD. In 3/4 HD patients tested with HS from Case D (HS-D), a PHA TI of less than 1 (suppression) was observed. This finding contrasted with those of NHL patients and normal subjects whose PHA-TI were always over 1 (stimulation) when HS-D was added. The significance of this factor is discussed. (41 Refs)

27. PERIPHERAL DESTRUCTION OF PLATELETS IN CHRONIC LYMPHOCYTIC LEUKEMIA: RECOGNITION, PROGNOSIS AND THERAPEUTIC IMPLICATIONS.

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Am J Med; 71(4):729-732 1981

In patients with chronic lymphocytic leukemia and depressed platelet counts, it is important to discriminate between the thrombocytopenia due to bone marrow replacement with abnormal lymphocytes and that caused by increased peripheral destruction of platelets. The former is due to progressive chronic lymphocytic leukemia and, as a Rai Stage IV, carries a poor prognosis. The latter, as illustrated in four patients seen at the National Cancer Institute, may be remediable by either splenectomy alone or splenectomy followed by immunosuppressive and antitumor therapy. In all four patients, survival was substantially longer than for patients whose condition was classified as Rai Stage IV. The importance of identifying the subgroup of patients with chronic lymphocytic leukemia with reversible thrombocytopenia is emphasized by these examples. (Author abstract) (11 Refs)

28. CHROMOSOMAL ABNORMALITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA: STRUCTURAL AND NUMERICAL CHANGES IN 234 CASES.

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Cancer Genet Cytogenet; 4(2):101-110 1981

Chromosomal abnormalities were found in cultured bone marrow and blood cells from 218/330 untreated patients and 16 treated patients with acute lymphoblastic leukemia. Five children and two adults (2.1% of the patients) had constitutional abnormalities, as opposed to 0.73% of 3,993 recently surveyed newborn infants. Of the 234 abnormal clones, 119 were pseudodiploid, 86 hyperdiploid, and 29 hypodiploid. Structural changes occurred in 204 cases, either alone (103) or combined with numerical changes (101); numerical changes alone accounted for 30 cases. The most common structural change was the presence of the Philadelphia chromosome associated with a translocation to chromosome 9. Chromosomes 1, 4, 6, 8, 11, and 14 also were involved in the structural changes. Lymphocyte marker studies in 182 cases showed that 72% were null cells, 19% T cells, and 9% B cells. Philadelphia chromosome-positive patients and those in the hyperdiploid category were all classified as having null cell leukemia. (8 Refs)

29. ANTAGONISTIC EFFECTS OF INTERFERONS ON THE CYTOTOXICITY MEDIATED BY NATURAL KILLER CELLS.

Trinchieri G, Santoli D, Granato D, Perussia B
Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104
Fed Proc; 40(12):2705-2710 1981

Human interferons (IFs) can induce a several-fold increase in the natural cytotoxicity of human lymphocytes on target cell lines. IFs increase the efficiency of cytotoxicity and the number of natural killer (NK) cells. In mixed cultures of lymphocytes and other tumor-derived or virus-infected cells, endogenous IF is produced, which mediates 70-90% of the observed cytotoxicity. The effect of If on target cells is antagonistic to its effect on lymphocytes: the susceptibility to lysis of cells treated with IF decreases. Whereas normal fibroblasts are protected by IF, virus-infected cells and most tumor-derived cells are not. The protective effect is specific for NK cell cytotoxicity: IF-treated target cells are lysed to the same extent as the untreated controls by antibody-dependent killer cells, by phytohemagglutinin-stimulated lymphocytes, by cytotoxic T lymphocytes, and by antibodies and complement. NK cells bind to IF-treated fibroblasts, but are unable to lyse them. The cytotoxic ability of NK cells is inactivated after interaction with normal fibroblasts, but not with IF-treated fibroblasts. Unlabeled, normal fibroblasts but not IF-treated fibroblasts complete for the cytotoxicity mediated by NK cells in 51-Cr-labeled target fibroblasts. IF, by stimulating very efficient, nonspecific cytotoxic cells, and by protecting normal cells from lysis, might render the NK cell system an inducible defense mechanism against virus-infected and tumor cells. (Author abstract) (28 Refs)

30. THE CYTOTOXIC EFFECT OF LYMPHOCYTES FROM PATIENTS WITH NASOPHARYNGEAL CANCER (NPC) AGAINST A NPC EPITHELIOID CELL LINE..

Lin Y, Zhao W, Zeng Y, Liu C, Hu G
Tumor Unit, Inst. Virology, Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Zhonghua Zhongliu Zazhi; 3(1):1-4 1981

Using a cell line derived from esophageal carcinoma (ECa109), the cytotoxic effects of lymphocytes obtained from NPC as well as other malignant and nonmalignant diseases were studied in vitro against an NPC epithelial cell line (CNE). Of 224 subjects tested, lymphocytes from 827. Of the NPC patients before radiotherapy exhibited cytotoxicity against CNE cells. However, lymphocytes from only 10% to 18%. Of other malignant and nonmalignant diseases showed cytotoxicity against CNE while lymphocytes from normal individuals showed only 6% cytotoxicity rate. (p less than 0.0001). Only 4% of NPC patients had cytotoxic lymphocytes against ECa109. The cytotoxic effects of lymphocytes from NPC patients were related to radiotherapy and clinical course, with a decrease from 82% to 23% cytotoxicity rate within 3 mo after radiotherapy and subsequent increase to 70% after 3 mo. The rate in patients who had metastasis or recurrence of disease after radiotherapy was 13%. It was also found that the lymphocyte cytotoxicity of NPC patients was related to EBV antibodies (VCA-IGA) reactivity. (14 Refs) (In CHI)

31. BIOLOGICAL MEASURES FOR THE FORMULATION OF A HOSPITAL PROGNOSTIC INDEX.

Harvey KB, Moldawer LL, Bistrian BR, Blackburn GL
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Am J Clin Nutr; 34(10):2013-2022 1981

Factors that might predict sepsis and mortality were investigated in 282 hospitalized patients referred for metabolic and nutritional therapy. Routine assessment parameters, including delayed hypersensitivity response to recall skin antigens, serum albumin and transferrin, total lymphocyte count, and anthropometric measurements were evaluated with respect to ultimate outcome. A discriminant function (0.91 (albumin) -1.00 delayed hypersensitivity -1.44 (sepsis) + 0.98 (diagnosis) -1.09) was developed having an overall predictive value for subsequent hospital mortality of 72%, a sensitivity of 74%, and a specificity of 66%. Serum albumin was found to be the best single indicator of concurrent sepsis and anergy, and predictor of mortality; an initial albumin less than 2.2 g/dl was associated with a greater than 75% chance of having concurrent anergy and sepsis and dying. An improvement in delayed hypersensitivity response was the most accurate predictor of an improved prognosis (overall predictive value 86%, sensitivity 93%, specificit y 63%). Thus, the use of serum albumin, delayed hypersensitivity response to recall skin antigens, clinical status, ie, septic or not septic, and presence or absence of cancer cachexia can serve to identify high risk patients in an objective fashion and evaluate the effectiveness of hospital therapy. This information may also assist the hospital team in allocation of resources. (Author abstract) (36 Refs)

32. RESULTS OF ADJUVANT BCG IMMUNOTHERAPY IN MALIGNANT MELANOMA.

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Arch Geschwulstforsch; 51(6):493-496 1981

Adjuvant BCG immunotherapy was tested in 114 patients with histologically confirmed malignant melanoma. Cases included 98 Stage I and 16 Stage II patients treated over a 5-yr period. All patients were tested for delayed cutaneous hypersensitivity to tuberculin and dinitrochlorobenzene (DNCB) and for blastogenic response of lymphocyte cultures to phytohemagglutinin and DNCB prior to and during treatment. BCG (6 x 10(8) colony forming units) was administered by scarification weekly for 3 mo, then monthly for 2 yr and every 3 mo thereafter for 3-5 yr. Results in BCG-treated patients were compared with a nonrandomized historical control group. Immunological examination showed no stimulation of immune response in Stage I or II cases. Recurrence and survival rates showed significant improvement in Stage I patients (20-30% survival rate), but not in Stage II patients. Results do not indicate BCG as optimum therapy for malignant melanoma, but further research is indicated. (8 Refs)

33. HODGKIN AND STERNBERG-REED CELL ANTIGEN(S) DETECTED BY AN ANTISERUM TO A CELL LINE (L428) DERIVED FROM HODGKIN'S DISEASE.

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Inst. Pathology, Christian Albrecht Univ., Kiel, W. Germany
Int J Cancer; 28(4):425-429 1981

Antisera to the cell line L428, derived from Hodgkin's disease, were raised in rabbits by injecting L428 cells iv and sc. The anti-L428 cell serum that did not react with HLA-DR was absorbed with tonsil cells plus acute myeloid leukemia cells or tonsil cells plus neutrophils, monocytes, and blood lymphocytes. Then it was tested for its ability to discriminate between L428 cells, Hodgkin and Sternberg-Reed cells, and various other cells. It was found that the anti-L428 cell serum absorbed with tonsil cells plus acute myeloid leukemia cells stained only L428 cells, Hodgkin and Sternberg-Reed cells, and neutrophils. The anti-L428 cell serum absorbed with tonsil cells plus neutrophils, monocytes, and blood lymphocytes reacted with L428 cells and Hodgkin and Sternberg-Reed cells from 13 cases of Hodgkin's disease. It did not react with any other cell type present in the blood or in lymphoid tissue or with cells from five cases of non-Hodgkin's lymphoma. The absorbed anti-L428 cell serum also failed to stain Daudi and HRIK cell line cells. We conclude that the anti-L428 cell serum defines an antigen that is apparently restricted in expression to L428 cells and Hodgkin and Sternberg-Reed cells. This is a strong indication that the L428 cell line cells are derived from Hodgkin and Sternberg-Reed cells. (Author abstract) (11 Refs)

34. HYPERFRACTIONATED TOTAL BODY IRRADIATION OR BONE MARROW TRANSPLANTATION: I. EARLY RESULTS IN LEUKEMIA PATIENTS.

Shank B, Hopfan S, Kim JH, Chu FC, Grossbard E, Kapoor L, Reid A, Chui C, Mohan R, Finegan D, O'Reilly RJ
Radiation Therapy Dept., Memorial Sloan-Kettering Cancer Cener, New York, NY, 10021
Int J Radiat Oncol Biol Phys; 7(8):1109-1115 1981

A hyperfractionated total body irradiation (TBI) regimen, with partial lung blocking, was developed to reduce the incidence of radiation interstitial pneumonitis (IP) in leukemia patients undergoing bone marrow transplantation. Hyperfractionated TBI (120 rads x 11; 3 x/day) decreased both IP incidence and deaths attributable to IP in 48 patients (mean age, 18 yr; range, 1.5-42 yr) with acute nonlymphocytic leukemia (ANLL), acute lymphocytic leukemia (ALL), and chronic myelocytic leukemia Sixteen patients (33%) developed IP, compared with 14/20 (70%) patients treated earlier with single dose irradiation (1,000 rads). The percentage of deaths related to IP decreased from 50% (10/10) in the earlier series to to 23% (11/48) with fractionated TBI. The 1-yr actuarial survival was 65% for ALL (16 patients) and 72% for ANLL (29 patients). Patients who died and patients who developed IP had a mean age of 25 yr. (11 Refs)

35. ADHERENT SUPPRESSOR CELLS IN THE BLOOD OF PATIENTS WITH BLADDER CANCER.

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J Urol; 126(4):457-460 1981

Patients with advanced bladder cancer frequently show a low mixed lymphocyte reaction. Depressed mixed lymphocyte reactions may be augmented by removing adherent cells, which appear to be monocytes. Since cancer patients often have a larger proportion of monocytes than normal individuals They may have suppression simply because of an increase in the number of these cells. This possibility was tested by adding increasing numbers of autologous irradiated monocytes or lymphocytes to mixed lymphocyte reactions depleted of adherent cells. The results showed that (1) monocytes from normal individuals increased the mixed lymphocyte reaction at optimal concentrations 3 to 4-fold and suppressed it at higher than optimal concentrations, (2) lymphocytes at equivalent concentrations were not suppressive and (3) monocytes from the cancer patients whose mixed lymphocyte reaction was low did not increase the mixed lymphocyte reaction at any concentration and suppressed it at lower concentrations than monocytes from the normal controls. These results suggest that suppression of the mixed lymphocyte reaction by patient monocytes was not owing to an over-all increase in their number but appeared to reflect a fundamental change in their suppressive function. (Author abstract) (10 Refs)

36. REACTIVITY OF MONOCLONAL ANTIBODIES WITH HUMAN MYELOID PRECURSOR CELLS.

Crawford DH, Francis GE, Wing MA, Edwards AJ, Janossy G, Hoffbrand AV, Prentice HG, Secher D, McConnell I, Kung PC, Goldstein G
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Br J Haematol; 49(2):209-217 1981

Five monoclonal antibodies have been tested for their ability to bind to myeloid precursor cells in normal human bone marrow. Indirect immunofluorescence and the fluorescence activated cell sorter was used to separate cells according to their reactivity for trial culture in vitro in order to grow granulocyte-macrophage colony forming cells (CFUc). Two antibodies (OKT3 and OKT11) which react strongly with bone marrow T lymphocytes were found to be unreactive with CFUc. YD1/23 reacts very strongly with both T and B lymphocytes but is only weakly reactive with CFUc. In contrast, OKT10 and YE2/36 did react with CFUc. The consequences of these findings and the potential clinical use of these antibodies in bone marrow transplantation are discussed. (Author abstract) (23 Refs)

37. PREOPERATIVE VALUE OF PERIPHERAL BLOOD LYMPHOCYTES IN COLORECTAL CANCER.

Devesa Mugica JM, Morales Castineiras V, Custardoy Motilva A, Enriquez Valens P, Avila C
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Rev Esp Enferm Apar Dig; 60(1):47-50 1981

The purpose of this study was the evaluation of the relationship between peripheral blood lymphocytes (PBL) and the stage of disease, location, carcinoembryonic antigen (CEA), short term prognosis in cases of local or disseminated disease. In the 18 mo period (1978-1979), 78 patients with colorectal adenocarcinoma had determinations of the PBL and CEA. The same was done with 42 control patients with benign diseases, excluding inflammations, allergies, autoimmune diseases, radiotherapy, corticotherapy or cytotoxic drugs. The values for urea and bilirubin were within normal limits. No statistically significant relationship was found with stage, location, CEA, but there was a clear cut relationship with the short term prognosis. The 4 mo to 2 yr survival time of patients with local or disseminated colorectal cancer improved when preoperatory PBL values were above 2,000 lymphocytes/ml. Of 19 death, 12 were due to sepsis. Lymphocytopenia is probably due to immunodeficient state. Authors suggest antibiotic and immuno prophylaxis for preoperative patients with lymphocytopenia in suspected advanced or disseminated neoplastic disease. (12 Refs) (In SPA)

38. STUDIES ON POSTOPERATIVE CHANGES OF NONSPECIFIC CELL-MEDIATED IMMUNITY IN PATIENTS WITH GASTRIC CANCER.

Yoshino J
Second Dept. Surgery, School Medicine, Mie Univ., Tsu-shi, Mie Prefecture 514, Japan
Nippon Geka Gakkai Zasshi; 82(4):355-367 1981

Postoperative changes of nonspecific cell-mediated immunity were studied in 82 patients with gastric cancer and 17 patients with benign gastric diseases. Among parameters studied preoperatively, lymphocyte count, phytohemagglutinin (PHA) lymphocyte response, and purified protein derivative (PPD) skin test were significantly depressed in the patients with advanced or recurrent carcinoma. No difference of corrected T-cell per cent in lymphocytes was found between normal adults and patients with benign gastric disease or gastric cancer. Lymphocyte count, PHA lymphocyte response, neuraminidase-treated sheep RBC (SRBC) rosette formation cell per cent, T-cell count, PPD and PHA skin tests were markedly depressed 2 wk after the operation and recovered to the preoperative value 2 mo after the operation in all the patients, regardless of the nature of the disease, or extension of tumor. Neither postoperative chemotherapy, nor tumor reduction affected these changes. In the long-term observation, however, depression of lymphocyte count, PHA lymphocyte response, and neuraminidase-treated SRBC rosette formation cellper cent reflected recurrence or exacerbation of tumor. Depression of neuraminidase-treated SRBC rosette formation cell per cent was particularly useful in precognition of recurrence or exacerbation of tumor. (31 Refs) (In JPN)

39. IMMUNOLOGICAL EFFECTS OF PROTEIN-BOUND KLEBSIELLAR POLYSACCHARIDE (PSK) IN PATIENTS WITH RETINOBLASTOMA: CHANGES IN T-CELL AND B-CELL SUBPOPULATIONS OF THE LYMPHOCYTES.

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Nippon Ganka Gakkai Zasshi; 85(5):403-409 1981

The immunological effects of PSK in patients with retinoblastoma were studied. Eighteen patients with retinoblastoma were treated by po administration of PSK. T-cell and B-cell subpopulations of the lymphocytes were counted before and after the treatment. In the patients with bilateral retinoblastoma, the mean of the T-cell subpopulation was significantly (p less than 0.001) lower than that of the control. On the other hand, in the patients with unilateral retinoblastoma, the mean of the T-cell subpopulation was similar to that of the control. The mean of the T-cell subpopulation in the patients with bilateral retinoblastoma increased significantly (p less than 0.05) after the treatment with PSK. The significance of the findings is discussed. (32 Refs) (In JPN)

40. EXPRESSION OF THE OKT MONOCLONAL ANTIBODY DEFINED ANTIGENIC DETERMINANTS IN MALIGNANCY.

Greaves M, Delia D, Sutherland R, Rao J, Verbi W, Kemshead J, Hariri G, Goldstein G, Kung P

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Int J Immunopharmacol; 3(3):283-299 1981

Cellular specificity in human leukemia of murine monoclonal antibodies OKT1, 3, 4, 6, 8, 9, 10, 11, and 11A were screened by microscopic and flow cytometric immunofluorescence methods and 125I-binding assays. Tests against malignant T cells showed a correlation between phenotype and clinical diagnosis. T cells from acute lymphoblastic leukemia (T-ALL) cells always showed an immature phenotype. Non-Hodgkin T lymphoma cells showed a cortical thymic phenotype. Both cell types appear to originate from T cell precursors. Cells from chronic T leukemias and cutaneous T lymphomas and leukemias that occur primarily in older adults showed mature T cell phenotypes. OKT11 and OKT11A reacted similarly with sheep E rosettes and appear to react to the same structures. Several T-ALL cell lines were modified in vitro to a more mature phenotype by 12-O-tetradecanoylphorbol 13 acetate or other inducers. This was demonstrated by binding of OKT1, 8, 9, 11, and other antibodies. OKT9 reacted preferentially with T leukemias, but was not T-specific, binding also to other leukemia cells and to other malignant tumor types. Cells induced to mature in vitro lost the OKT9 determinant. OTK9 bound to a receptor that may be a marker for malignancy. OKT10 bound to leukemias and normal bone marrow cells of the myeloid and B cell lineages. OTK6 bound to neuroblastoma cells. (43 Refs)

41. 'NON'-MALIGNANT TUMORS.

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Int J Radiat Oncol Biol Phys; 7(8):1129-1130 1981

Use of the terms non-Hodgkin's lymphoma (NHL), nonseminomatous testicular tumor, and 'non-small cell' carcinoma of the lung (NSCLC) is criticized. The term NHL lumps together such disparate diseases as mediastinal T-cell lymphoma, nodular lymphoma of the middle aged, and primary lymphomas of the stomach, thyroid, testis, and Waldeyer's ring. Testicular carcinomas have long been distinguished from testicular seminomas, and there is no need for a new term. NSCLCs are all less responsive to chemotherapy than small cell tumors, but there are important differences among the histopathologic types. (8 Refs)

42. CLINICAL SIGNIFICANCE OF CHROMOSOMAL ABNORMALITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA.

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Cancer Genet Cytogenet; 4(2):111-137 1981

Correlations between chromosome classification and clinical and hematologic findings at diagnosis, and the relation between karyotype and response to treatment, were examined in 173 adults and 157 children with acute lymphoblastic leukemia (ALL). All patients with a modal number greater than 46 and/or the Philadelphia chromosome had non-T-, non-B-cell ALL; children and adults with chromosome translocations and high initial WBC counts tended to have B-cell ALL. Patients with a normal karyotype or pseudodiploidy accounted for most of the T-cell ALL cases. The complete response rate to treatment was 91% for children and 65% for adults. ALL patients with a modal number greater than 50 responded best, and children in this group frequently appeared to be cured. Patients without chromosomal abnormalities or a 6q- also did well. In contrast, patients with t(4;11) or t(8;l4) ALL responded poorly and had the shortest survival. Of the non-T, non-B ALL patients, those with a modal number less than 46 and the Philadelphia chromosome had the poorest prognosis and those with a modal number greater than 50, pseudodiploidy, or no abnormalities had the best prognosis. Karyotype was a prognostic variable independent of other risk factors such as age, WBC count, and FAB (Franco-American-British) classification. (4 Refs)

43. GLUCOCORTICOID RECEPTORS IN LYMPHOID TUMORS.

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Cancer Res; 41(11,part2):4861-4862 1981

There is a range of levels of glucocorticoid receptor numbers seen in the various subclasses of acute lymphatic leukemia (ALL). This variability cannot be explained by the known correlation between active cell proliferation and an increase in the number of receptors, since the tumors with the highest growth fraction (ie, Burkitt's lymphoma and T-cell leukemia) tend to have lower av receptor numbers than do tumors with lower growth fractions such as common ALL. All clinical specimens from patients with lymphatic leukemia have some measurable level of glucocorticoid receptors; therefore, the resistance seen in vivo cannot be explained by the lack of receptors. However, there has been a positive correlation, in our hands, with receptor level and prognosis. On the basis of in vitro models, it is proposed that perhaps the high receptor cell lines (ie, common ALL of childhood) have relative stability of their genetic material making glucocorticoid-resistant mutations less likely to occur in patients with these cells than in low-receptor cell lines (ie, T-cell leukemia). This greater genetic variability in the low-receptor lines could account for the earlier emergence of clinical glucocorticoid resistance in these patients. (Author abstract) (15 Refs)

44. SUMMARY: SYMPOSIUM ON EPSTEIN-BARR VIRUS-INDUCED LYMPHOPROLIFERATIVE DISEASES IN IMMUNODEFICIENT PATIENTS.

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Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden

Cancer Res; 41(11,part1):4302-4304 1981

The possibility that the X-linked lymphoproliferative syndrome, renal transplant lymphomas, and other lymphomas in immunodeficient patients originate in proliferating Epstein-Barr virus (EBV)-carrying lymphoid cells is discussed. Evidence for this association included the detection of EBV nuclear antigen (EBNA) in virus-transformed cells and changes in EBV antibody titers in immunodeficiency conditions. Defects of the T-cell system were associated with increased titers against EBV early and viral capsid antigens and decreased anti-EBNA titers. Chronic infectious mononucleosis patients and X-linked lymphoproliferative syndrome patients showed marked impairment of all effector mechanisms involved in the rejection of EBV-carrying cells. (23 Refs)

45. CELL-MEDIATED IMMUNE REACTIONS IN THREE PATIENTS WITH MALIGNANT LYMPHOPROLIFERATIVE DISEASES IN REMISSION AND ABNORMALLY HIGH EPSTEIN-BARR VIRUS ANTIBODY TITERS.

Masucci MG, Szigeti R, Ernberg I, Bjorkholm M, Mellstedt H, Henle G, Henle W, Pearson G, Masucci G, Svedmyr E, Johansson B, Klein G

Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden

Cancer Res; 41(11,part1):4292-4301 1981

Two patients with Hodgkin's disease in remission and one chronic lymphatic leukemia patient with extraordinarily high anti-Epstein-Barr virus (EBV) (viral capsid antigen) antibody titers (greater than 10,000) were selected to study a spectrum of cell-mediated immune responses, including natural killer, interferon-boosted killer, antibody-dependent lymphocytotoxicity, and T-cell-mediated reactions. The purpose was to compare these reactions in patients with immunosuppression and a high EBV load who can hold their EBV-carrying cells under control with the corresponding reactions in patients with EBV-carrying lymphoproliferative disease. In contrast to the latter group, the three patients of the present study showed a less profound and less general suppression of the immune responses. Multiple effector mechanisms probably safeguard against the proliferation of EBV-transformed B-cells. Clinically manifest EBV-carrying lymphoproliferative disease occurs only in very severe immunodeficiencies effecting multiple effectors. (Author abstract) (44 Refs)

46. EPSTEIN-BARR VIRUS IN A MALIGNANT LYMPHOPROLIFERATIVE DISORDER OF B-CELLS OCCURRING AFTER THYMIC EPITHELIAL TRANSPLANTATION FOR COMBINED IMMUNODEFICIENCY.

Reece ER, Gartner JG, Seemayer TA, Joncas JH, Pagano JS

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Cancer Res; 41(11,part1):4243-4247 1981

A fatal disseminated polyclonal malignant lymphoproliferative disorder of B-cells (immunoblastic sarcoma) developed shortly after a second thymic epithelial peritoneal implant in a 5-yr-old girl with combined immunodeficiency. The immunodeficiency was characterized by low T-cell numbers and function, very low levels of thymic hormone, dysgammaglobulinemia, and an inability to mount a primary antibody or cell-mediated response to new antigens. At necropsy, the thymus fulfilled morphological criteria for thymic dysplasia. Epstein-Barr virus (EBV) antigen and DNA were identified in neoplastic infiltrates in the lymph nodes and thymus by immunofluorescence for the EBV nuclear antigen and by EBV-specific complementary RNA/DNA hybridization. No antibodies to nuclear antigen, early antigen, or viral capsid antigen of EBV were identified in the serum. The concurrence of these events suggests that the thymic epithelial implant itself may have been instrumental in the pathogenesis of this neoplasm. It is proposed that the thymus may have provided factors which indirectly potentiated the proliferation of EBV-infected B-cells, possibly by induction of nonspecific T-helper cells and perhaps through other thymic humoral factors. It is suggested that some forms of immunoblastic sarcoma, even when polyclonal, and especially those which arise in immunocompromised hosts, may, in some instances, represent an opportunistic form of EBV-induced B-cell neoplasia. (Author abstract) (39 Refs)

47. T-CELL RESPONSE TO B-CELLS AND EPSTEIN-BARR VIRUS ANTIGENS IN INFECTIOUS MONONUCLEOSIS.

Klein E, Ernberg I, Masucci MG, Szigeti R, Wu YT, Masucci G, Svedmyr E

Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden

Cancer Res; 41(11,part1):4210-4215 1981

After Epstein-Barr virus (EBV) infection in vivo, B-cells with latent virus infection persist indefinitely through life. These cells grow in vitro on explantation and can be established as immortal B-cell lines. To reconcile the unlimited growth potential in vitro with the maintenance of a low proportion of B-cells infected by EBV in vivo, a strict in vivo control mechanism has to be postulated. Certain aspects of this control are apparent when the primary infection is followed by infectious mononucleosis. This is characterized by lymphocytosis and the presence of activated T-cells. The T-cell proliferation is probably the manifestation of the immune response against EBV antigens. However, the reaction of T-cells upon encounter of B-blasts is also likely to contribute to the events. At present, it is difficult to detect an EBV-specific component in the action of the T-cells in the acute phase of mononucleosis exerted on B-cells. However, for the clinical course of the disease the activation of T-cells is important. The activated T-cells may control and also eliminate the B-cells infected by EBV. In addition to the immunity which develops during the disease, the immunoregulatory mechanism is likely to have a role in the inhibition of B-cell proliferation. (Author abstract) (52 Refs)

48. LYMPHOCYTE DYSFUNCTION IN CHRONIC GRAFT-VERSUS-HOST DISEASE.

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Dept. Medicine, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Blood; 58(4):746-751 1981

Three recipients of HLA-identical bone marrow transplants developed chronic graft-versus-host disease (cGVHD) and hypergammaglobulinemia. All three had evidence of abnormal B-lymphocyte function, including a polyclonal increase in Ig, antinuclear antibodies, rheumatoid factor, lymphocytotoxins, and increased immune complexes. T-lymphocyte function was also abnormal, including decreased mitogen reactivity and delayed cutaneous hypersensitivity. The cellular basis of these immune abnormalities was studied in an in vitro system in which we analyzed spontaneous pokeweed mitogen (PWM) driven Ig synthesis. Multiple defects in both T- and B-lymphocyte function were detected. In contrast to normal B cells, circulating B cells from all three patients with cGVHD spontaneously synthesized in vitro greater than 200 ng of IgG and in two of the three greater than 175 ng of IgM. This increase in spontaneous Ig synthesis was not due to a deficiency of regulatory cells, since T cells from the three patients suppressed spontaneous Ig synthesis in a normal fashion. In contrast to this increased spontaneous Ig synthesis, the response of the patients' B cells to PWM-driven Ig synthesis was normal. Using the PWM system we demonstrated several defects in these patients' T cells, including increased suppressor activity and decreased helper cell activity. These data indicate that some patients with cGVHD have multiple defects in both T- and B-cell function that may contribute to their profound immune deficiency. (Author abstract) (40 Refs)

49. TREATMENT OF MALIGNANT TUMORS IN BIOCLEAN ROOMS (LAMINAR AIR FLOW AND CONVENTIONAL BIOCLEAN ROOMS) (MEETING ABSTRACT).

Ohira M, Omiya A, Hirose M, Ise T
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Program and Abstracts of the 84th Annual Congress of Japan Pediatric Society held in Tokushima, Japan, 15-17 May, 1981. Japan Pediatric Society, Tokyo 160, Japan, 398 pp., 1981.

A laminar air flow bioclean room and two conventional bioclean rooms built in 1979 and 1980 were used to treat patients with malignant tumors axenically. The patients treated in these rooms were 1 to 11 yr old, two had acute lymphatic leukemia, four had acute myelogenous leukemia, one had acute myelogenous monocytic leukemia, two had T-cell lymphoma, one had retinoblastoma, one had a yolk-sac tumor and one had rhabdomyosarcoma. The patients who were to be in the laminar air flow bioclean room (class 100), had their hair cut short, were bathed in Hibitane, were given an axenic diet, were given large doses of a nonabsorbed oral antibiotic, and were sterilized by antibiotic nebulizers and ointment. The family was allowed to care for the patient only when necessary and only through a vinyl sheet. The conventional bioclean room was disinfected by spraying chemicals in the room and wiping it clean. Food was not sterilized and the family was allowed to care for the child. In the laminar air flow bioclean room, although the peripheral WBC count was less than 500 for a long time, the number of days that the child had a fever was less than that for a child in the general hospital room, and no serious infectious diseases developed. The conventional bioclean room was also effective in preventing infectious respiratory diseases, and potent multiple drug therapy could be performed easily. The laminar air flow bioclean room is essential for patients who have diseases accompanied by extreme immunosuppression, but the conventional bioclean room can be used even by seriously ill children. (no Refs) (In JPN)

50. EFFECT OF HIGH-DOSE THYMIDINE INFUSIONS IN PATIENTS WITH MYCOSIS FUNGOIDES.

Kufe DW, Wick MM, Moschella S, Major P
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Cancer; 48(7):1513-1516 1981

The antitumor effect of thymidine has been demonstrated in patients with leukemia and lymphoma. This report summarizes the treatment of three patients with mycosis fungoides, a chronic T-cell lymphoma. Four courses of thymidine (75 g/m2/day) were administered by continuous infusion for 4-7 days. Steady-state serum thymidine levels were in the range of 1-3 mM. Associated toxicities were minimal and consisted of mild headache and anorexia. Myelosuppression was manifested by transient declines in the peripheral WBC count. One patient had extensive clearing of diffuse erythematous plaques on the trunk and extremities that persisted for over 1 mo. A second patient had partial clearing of plaques that persisted for 2 wk following therapy and a third patient had a minimal response with 25% reduction in lymphadenopathy and noduloulcerative lesions. These responses indicate the effectiveness of thymidine as a single agent in the treatment of mycosis fungoides. (Author abstract) (17 Refs)

51. T-LYMPHOCYTES IN B-CELL CHRONIC LYMPHOCYTIC LEUKAEMIA.

Foa R, Catovsky D, Lauria F, Zafar MN, Galton DA
Istituto di Medicina Interna, la Cattedra di Patologia Speciale Medica, Corso Polonia, 14, 10126 Torino, Italy
Haematologica (Pavia); 66(1):105-116 1981

Functional properties of T-lymphocyte cells in B-cell chronic lymphocytic leukemia (B-CLL) were studied, including distribution of the major T-lymphocyte subsets: helper (Tmu) and suppressor (Tgamma) cells. Isolated T-lymphocytes in B-CLL failed to transform normally when cultured in the presence of the plant mitogen phytohemagglutinin (PHA) in 4/9 cases. T-colony-forming capacity was impaired in 12/16 cases. Significant imbalance in T-cell subset distribution was demonstrated in patients tested: the proportion of Tgamma cells is significantly higher in more advanced stages of B-CLL. Percentage of Tmu cells appears not related to disease stage; it was significantly reduced in most patients. The role of T-lymphocyte functional abnormalities in B-CLL is discussed, with review of findings reported in the literature. (53 Refs)

52. PROGNOSTIC SIGNIFICANCE OF THE T-CELL-MARKER IN CHILDHOOD ACUTE LYMPHATIC LEUKEMIA.

Pluss HJ, Joller PW, Hitzig WH
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Schweiz Med Wochenschr; 111(41):1527-1531 1981

Of 58 children with acute lymphatic leukemia who had undergone marker studies of blasts, only 6 (10%) had greater than 30 E+ blasts. Of these, five had a high WBC and organomegaly, but only two suffered a fatal course. Two more have been in CCR for over 5 yr despite other risk factors. Patients with less than 30% E+ cells did not differ from common ALL patients clinically or in their response to treatment. However, three older children with Hp-positive but E negative blasts had a very high WBC and died without having remission. Only standardized marker studies, treatment and follow-up of a large series of ALL patients will show the importance to be attached to these and other T-cell markers compared with the better-known clinical and hematologic risk factors. (Author abstract) (3 Refs) (In GER)

53. LYSIS OF HUMAN B-LYMPHOCYTE-DERIVED LYMPHOMA/LEUKEMIA CELLS OF ESTABLISHED CELL LINES BY INTERFERON-ACTIVATED NATURAL KILLER (NK) CELLS.

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Int J Cancer; 28(4):459-468 1981

Cultured cell lines derived from malignant Epstein-Barr virus (EBV)-negative B cells, and representative of the more common types of naturally occurring non-Hodgkin lymphomas and related leukemias, were found to be sensitive to lysis by human natural killer (NK) cells. The observed lysis of such cell lines was mediated by a population of interferon-augmentable, FcR-positive, non-adherent lymphoid cells, which were also able to kill the 'standard' NK targets K562 and Molt-4. When the NK susceptibility of the neoplastic, EBV-negative B cells was compared to that of diploid, EBV-carrying, non-neoplastic B lymphoblastoid cell lines (BLCLs) and of the 'standard' NK target K562, several distinct patterns were observed. The killing of the neoplastic B cell lines was significantly less than that of K562, but significantly greater than that of the EBV-derived BLCLs of non-neoplastic origin. An additional finding was a similar NK susceptibility profile for the neoplastic, true histiocytic cell line U-937 (ie, K562 greater than U937 greater than BLCLs). Furthermore, all cell lines, with the exception of the BLCLs, could effectively compete for the observed killing in cold target inhibition assays. The implications of these findings are discussed in relation to both neoplastic and non-neoplastic targets of NK lysis. (Author abstract) (49 Refs)

54. DOCUMENTATION OF EPSTEIN-BARR VIRUS INFECTION IN IMMUNODEFICIENT PATIENTS WITH LIFE-THREATENING LYMPHOPROLIFERATIVE DISEASES BY EPSTEIN-BARR VIRUS COMPLEMENTARY RNA/DNA AND VIRAL DNA/DNA HYBRIDIZATION.

Saemundsen AK, Purtilo DT, Sakamoto K, Sulllivan JL, Synnerholm AC, Hanto D, Simmons R, Anvret M, Collins R, Klein G
Dept. Tumor Biology, Karolinska Inst., 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4237-4242 1981

Tissues from patients thought to have Epstein-Barr virus (EBV)-induced lymphoproliferative diseases were probed for EBV genomes using two independent hybridization techniques. Tissues from six patients with the X-linked lymphoproliferative syndrome, all five renal allograft recipients with immunoblastic sarcoma, and eight patients with diverse types of immunodeficiency and lymphoproliferative diseases such as fatal infectious mononucleosis or malignant lymphoma associated with antecedent immunodeficiency contained significant numbers of EBV genome equivalents per cell. The use of two hybridization probes is recommended to confirm the presence of EBV genomes. The finding of significant numbers of EBV genomes in tissues from patients with immunodeficiency suggests that EBV is the etiological agent of the associated lymphoproliferative diseases. (Author abstract) (53 Refs)

55. EPSTEIN-BARR VIRUS-SPECIFIC SEROLOGY IN IMMUNOLOGICALLY COMPROMISED INDIVIDUALS.

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Cancer Res; 41(11,part1):4222-4225 1981

Since B-lymphocytes are targets and a continuing habitat of Epstein-Barr virus (EBV) and the cell-mediated immune system becomes secondarily involved, one may anticipate that primary and persistent EBV infections in immunologically compromised individuals take unusual courses. Depending on the immunological defect, the clinical, hematological, and serological responses to primary EBV infections may be more or less pronounced than in immunologically competent patients. Infectious mononucleosis has per se an immunosuppressive effect which may enhance a preexisting immune defect. The persistent latent viral carrier state which regularly ensues after the primary EBV infection may become decontrolled by immunosuppressive diseases or therapy, leading rarely to illnesses referable to the virus but often to increases in the titers of antibodies to viral capsid and early antigens and/or declines in the antibody titer to EBV-associated nuclear antigen. Absence or dysfunction of different WBC subpopulations may account for the differential changes in antibody patterns. (Author abstract) (42 Refs)

56. INTRODUCTION TO EPSTEIN-BARR VIRUS AND LYMPHOPROLIFERATIVE DISEASE IN IMMUNODEFICIENT INDIVIDUALS.

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Dept. Pathology and Lab. Medicine, Univ. Nebraska Medical Center, Omaha, NE, 68105
Cancer Res; 41(11,part1):4209 1981

Attention is directed to accompanying articles on the possible roles of Epstein-Barr virus (EBV) and immunodeficiency in lymphoproliferative diseases (LPD). The authors have sought to develop criteria for establishing involvement or noninvolvement of EBV in LPD in immunodeficient patients. (11 Refs)

57. CELLULAR IMMUNE DEFECTS TO EPSTEIN-BARR VIRUS-DETERMINED ANTIGENS IN YOUNG MALES.

Masucci MG, Szigeti R, Ernberg I, Masucci G, Klein G, Chessels J, Sieff C, Lie S, Glomstein A, Businco L, Henle W, Henle G, Pearson G, Sakamoto K, Purtilo DT
Dept. Tumor Biology, Karolinska Inst., S 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4284-4291 1981

Three males with the X-linked lymphoproliferative syndrome (XLP) with hypo- or agammaglobulinemia following Epstein-Barr virus (EBV) infection and two males with the chronic mononucleosis syndrome were investigated for immune responses to EBV-determined antigens. Males with XLP showed profound cellular immune defects. Markedly diminished responses of natural killer cell and interferon-activated killer cell activities and impaired WBC migration inhibition responses to phytohemagglutinin were determined in patients with XLP. The two patients with chronic mononucleosis showed less severe defects. All patients showed partial or complete impairment of their EBV-specific immune responses as measured by WBC migration inhibition. EBV-specific antibodies were markedly diminished against EBV-associated nuclear antigen, early antigen, and viral capsid antigen in males with XLP. In contrast, patients with chronic mononucleosis had elevated antibodies to most EBV-specific antigens. Individuals with life-threatening EBV-induced lymphoproliferative disorders may exhibit multiple defective immune mechanisms against the virus. (Author abstract) (44 Refs)

58. KINETICS OF SPONTANEOUS ROSETTE FORMATION IN CANCER OF THE STOMACH.

Kurtenkov OA, Miliakhina LM

Inst. Experimental and Clinical Medicine, Tallin, USSR

Lab Delo; (8):491-493 1981

Kinetics of spontaneous rosette formation (E-RFU) was studied in 12 patients with cancer of the stomach, 8 patients with ulcer or gastritis, and 10 healthy controls. In controls, the number of E-RFU reached the max after 45-90-min incubation, compared with characteristic shift to the right in cancer patients. The most pronounced differences in the rate of rosette formation between controls and can cer patients were recorded after 15-120-min incubation. There was no differences in the number of total and active E-RFU. (11 Refs) (In RUS)

59. FC AND COMPLEMENT RECEPTORS ON MALIGNANT TUMOR CELLS.

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Cancer; 48(8):1761-1767 1981

The Fc-C'-receptor-positive cells were investigated in tumor cell suspensions from 196 malignant tumors. The number of EA (Fc) and EAC' (C') rosettes was determined; the rosette-forming cells were identified cytologically, the cell suspensions were exposed to carbon particles, and they were grown in tissue culture. The results suggest that Fc or C' receptors might be present in malignant tumor cells as well as in host defense (inflammatory) cells invading the tumor. (Author abstract) (37 Refs)

60. IMMUNOLOGIC DETECTION OF EAR-NOSE-THROAT TUMORS.

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Laryngol Rhinol Otol (Stuttg); 60(8):402-404 1981

The diagnostic efficacy of the macrophage electrophoretic mobility (MEM) test with human encephalitogenic protein (HEP) as antigen was studied in 31 patients with ear-nose-throat tumors, 108 patients with tumors of other localizations, and 116 tumor-free controls. Laryngeal carcinoma was diagnosed in 21/31 patients, hypopharyngeal carcinoma in 2, tonsillar carcinoma in 2, carcinoma of the tongue in 2, and other tumors in 4. Colorectal carcinoma was diagnosed in 27/108 patients with other tumors, gastric carcinoma in 32, hypernephroid carcinoma in 6, breast carcinoma in 18, and other tumors in 25. The MEM test was false positive in 17.7% of the tumor-free controls, ie, the selectivity was 82.3%. The MEM test was positive in 77.8-100% of the 139 tumor patients, av 83.7%. The av percentage of positive MEM tests was 89.3% for the 31 patients with ear-nose-throat tumors. (10 Refs) (In GER)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

61. THE ROLE OF INTERLEUKIN-2 (IL-2) IN THE DIFFERENTIATION OF CYTOTOXIC T CELLS: THE EFFECT OF MONOCLONAL ANTI-IL-2 ANTIBODY AND ABSORPTION WITH IL-2 DEPENDENT T CELL LINES.

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J Immunol; 127(4):1323-1328 1981

A variety of approaches, including the use of a monoclonal antibody, have indicated that the lymphokine interleukin 2 is a necessary and sufficient mediator for initiating cytotoxic T cell differentiation in vitro. Mitogen (Con A, PHA) stimulation of spleen cells and K/D or I region stimulation in primary MLC all led to IL-2 production, as measured by the growth of an IL-2 dependent T cell clone, and to the production of a 'helper' factor necessary for cytotoxic T lymphocyte (CTL) differentiation against metabolically inactivated stimulator spleen cells. Several lines of evidence suggested that the IL-2 activity and CTL 'helper' activity were due to a single molecular entity. These included the observations that: (i) there was a linear relationship (R = 0.99) between IL-2 activity and relative CTL 'helper' activity regardless of the preparation used (purified IL-2; MLC, or mitogen-induced supernatants). (ii) Absorption of MLC supernatants with T cell 'blasts' or with IL-2 dependent T cell lines concomitantly removed both IL-2 and CTL 'helper' activities, (iii) IL-2 activity purified by isoelectric focusing, or by polyacrylamide gel electrophoresis, displayed CTL 'helper' activity. (iv) Both CTL 'helper' and IL-2 activities were neutralized by a monoclonal antibody directed against IL-2. (Author abstract) (21 Refs)

62. CYTOTOXIC T CELLS IN SMALL INTESTINE EPITHELIAL, LAMINA PROPRIA AND LUNG LYMPHOCYTES.

Davies MD, Parrott DM

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Immunology; 44(2):367-371 1981

We have examined the development of specific cytotoxic T-cell activity in the lungs and the epithelium and lamina propria of the small intestine following tumor cell inoculation by sc or ip routes. After an ip injection of tumor cells, large amounts of cytotoxic activity are detectable in the lungs and lamina propria. In comparison, the epithelial lymphocytes of the small intestine display low cytotoxic activity. After a sc injection, little cytotoxicity is detectable except in the lungs and the development of such cytotoxicity has a much shorter time course compared with that induced by an ip inoculation of tumor cells. The data indicate a marked difference in the functional capacity of lymphocytes from the epithelium and lamina propria of the small intestine. (Author abstract) (17 Refs)

63. PATHOGENESIS OF POST-IRRADIATION INFECTIONS. I. YERSINIA ENTEROCOLITICA ADMINISTERED TO NORMAL AND IRRADIATED RATS.

Bazin H, Platteau B, Janssens M, Wauters G
Experimental Immunology Unit, Lab. Microbiology, Faculty Medicine-Univ. Louvain, Clos Chapelle aux Champs, 30-B-1200 Brussels, Belgium
Int J Radiat Biol; 40(3):277-282 1981

Infections after irradiation can be due to a great variety of microorganisms many of which are normally non-pathogenic or conditionally pathogenic for the host. The strain of Yersinia enterocolitica used was not pathogenic to a variety of unirradiated rats nor to athymic or B lymphocyte deprived, macrophage depleted rats, nor to normal rats irradiated by 5.7 Gy 24 hr before. However similarly irradiated rats receiving Y enterocolitica 5 or 10 days later showed a substantial mortality. It is concluded that the radiosensitive mechanism for protection against Y enterocolitica is not humoral nor cellular immunity as mediated by T and B lymphocytes or macrophages. (Author abstract) (21 Refs)

64. RELATION OF BOVINE LEUKOSIS VIRUS PRODUCTION ON CELL GROWTH CYCLE.

Takashima I, Olson C
Faculty Veterinary Medicine, Hokkaido Univ., Sapporo, Japan
Arch Virol; 69(2):141-148 1981

The cell cycle of fetal lamb kidney (FLK) cultures chronically infected with bovine leukosis virus was synchronized by double thymidine block. The synchronized FLK cells were examined for production of BLV antigen and virion release by cytoplasmic immunofluorescence and syncytia forming assay, respectively. The production of BLV antigens was increased during S and G2 phases and was decreased during M and G1 phases. BLV release was associated with the M phase of FLK cells. Short term lymphocyte cultures from BLV infected cattle were treated with hydroxyurea and mitomycin C. The expression of BLV antigen and DNA synthesis of PHA stimulated lymphocytes was inhibited by both drugs. (Author abstract) (21 Refs)

65. CHANGES OF LEUKOCYTE AND LYMPHOCYTE VALUES AND OF CYTOTOXICITY IN TUMOR-CARRYING RATS IN DEPENDENCE ON A LOCAL IRRADIATION AND INCREASE OF CAMP LEVEL, RESPECTIVELY.

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Radiobiol Radiother (Berl); 22(3):331-335 1981

The effects of various therapeutic measures on aspects of immune response in tumor-bearing rats were studied. Rats of 200-250 g received 10(8) cells of Jensen sarcoma by injection into the thigh. Treatment consisted of irradiation (21 Gray, administered in 3-Gray fractions), raising of cyclic (c) (cAMP) level (by administration of antitumor substances Dopaflex (D), Amantadin (A), and measles vaccine), or a combination of the two. Radiation dose was 21 Gray, administered in 3-Gray fractions beginning 2 days after tumor cell injection. A combination of 50 mg D and 6 mg A/kg body wt was administered on the first day of treatment, with a dose of 100 mg D and 20 mg A/kg body wt on successive days. Measles vaccine (dose 10,000 TCD50/day) was administered on days 1, 3, and 5 with D and A treatment. Development of the tumor cells was accompanied by a reduction in total WBC, lymphocyte, and T-cell subpopulation counts. B-cell counts rose. The cytotoxicity of WBC against tumor cells was also reduced. These effects were dependent on tumor size. Radiation treatment was followed by a decrease in the same counts. Treatments to raise cAMP reduced the effects in animals still showing tumors, and eliminated them in animals showing no tumors after irradiation. (29 Refs) (In GER)

66. SENSITIVITY OF CLONED HIGH- AND LOW-METASTATIC MURINE LEWIS LUNG TUMOR CELLS TO LYSIS BY CYTOTOXIC AUTOREACTIVE CELLS.

Olsson L, Kiger N, Kronstrom H
Medical Dept. A., State Univ. Hosp., 9 Blegdamsvej, Dk-100 Copenhagen, Denmark
Cancer Res; 41(11,part1):4706-4709 1981

Cloned malignant cell lines from primary tumor sites (2 lines) and from a lung metastatic focus (1 line) were established 14 and 28 days after sc inoculation of Lewis lung tumor cells into C57BL/6 mice. Cloning was done in semisolid agarose culture medium and individual clones expanded in liquid medium. In vivo malignancy of the three lines was assured by graft experiments to healthy C57BL/6 recipients. Morphology, cloning efficiency in agarose, and growth rate were the same for all three lines. However, the cloned line from a metastatic focus had a higher metastatic rate (number of lung metastases per 10(5) injected tumor cells) compared to the two other cell lines. T-lymphocyte-depleted mononuclear spleen cells from mice grafted with tumor cells 2 to 4 wk previously were found to be cytotoxic to cells from all three lines, whereas unfractionated mononuclear spleen cells from the same animals had weak or no cytotoxic activity. The cytotoxicity of T-lymphocyte-depleted spleen cells was found to include other malignant and nonmalignant target cells of C57BL/6 origin, but not allogeneic cells. In mixing experiments, splenic T-lymphocytes inhibited the cytotoxic activity of non-T-lymphocytes. The high- and low-metastatic tumor cell lines were found to be equally sensitive to lysis by T-cell-depleted spleen cells, suggesting that the effector cells (cytotoxic autoreactive cells) may have a significant antineoplastic potential. (Author abstract) (23 Refs)

67. TUMOURS OF THE MUCOSA OF THE ETHMOID IN PIGS.

Rajan A, Sulochana S, Vikram Reddi M, Sreekumaran T, RamachandranKM, Maryamma KI, Valsala KV
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Indian J Cancer; 18(3):202-205 1981

Tumors of the mucosa of the ethmoid occurred in 30 large white Yorkshire pigs from 1965 to 1968. Detailed study was made of 26 cases. Ages of the animals ranged from 1.5 to 4 yr. The disease was characterized by slight respiratory difficulty and nasal discharge. Intermittent epistaxis was an early symptom. Swelling of the forehead was a late symptom, followed in 1-2 mo by death. Tumors were found to arise from the ethmoturbinal region and invade the frontal sinus. Perforation of the lamina cribrosa with invasion of the brain occurred in 11 cases. Tumors included 11 adenocarcinomas and 14 squamous cell carcinomas. Adenocarcinomas contained acinar spaces lined with proliferating nonciliated columnar cells. Sheets of undifferentiated proliferating epithelial cells occurred in focal areas. Stromal tissue was infiltrated by lymphocytes and macrophages. A transition from columnar to squamous cells was noted in some cases, suggesting Bowman's gland as the origin of both tumor types. Occurrence and later recurrence of tumors seems related to the occurrence of aflatoxin in feed. (14 Refs)

68. THE EFFECT OF PHOTOCHEMOTHERAPY (PUVA) ON CELL MEDIATED IMMUNITY IN THE GUINEA PIG.

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J Invest Dermatol; 77(4):377-380 1981

Guinea pigs were injected ip with 8-methoxypsoralen (8-MOP) and afterwards the shaved right flank was irradiated with UV-A. This treatment was performed daily for 14 days. Seven days after treatment started they were immunized with ovalbumin in Freund's complete adjuvant and 7 days later skin tested with ovalbumin on the unirradiated left flank. Photochemotherapy (8-MOP plus UV-A) did not alter the total WBC or the proportion of lymphocytes or granulocytes. However, this treatment significantly depressed the delayed hypersensitivity reaction to ovalbumin; nonspecific inflammation, induced by id turpentine, was not altered. In addition, treatment with 8-MOP alone suppressed the skin reaction to ovalbumin, but not to the same extent as treatment with 8-MOP and UV-A. 8-MOP plus UV-A had not effect on macrophage migration inhibition factor but it did significantly depress mitogen and antigen specific lymphocyte transformation. (Author abstract) (15 Refs)

69. MECHANISM OF SUPPRESSION ON CELLULAR IMMUNITY IN EXPERIMENTAL BRAIN TUMOR RATS.

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Neurol Surg; 9(4):503-508 1981

The mechanism of suppression of cellular immunity was studied in rats inoculated in the caudate nucleus with cells from a 3-methylcholanthrene-induced fibrosarcoma. When spleen cells from the brain tumor rats were added to a phytohemagglutinin (PHA) blastogenesis system, the normal lymphoproliferative response was impaired as early as day 3 and until day 9 after inoculation. After depletion of glass adherent cells, the residual spleen cells did not suppress PHA lymphoblastogenesis. Spleen cells remaining after depletion of T cells by anti-T cell sera and complement continued to suppress the normal PHA response. Glass adherent cells phagocytized latex particles. Results suggested that the cell responsible for suppression of PHA lymphoblastogenesis was a macrophage; suppressor T cells did not seem to play a role in the suppression of PHA responses. The sera from brain tumor rats did not inhibit the response of lymphocytes to PHA, indicating that suppressive serum factors probably were negligible. (45 Refs) (In JPN)

70. 2-CYANOETHYL UREA AND ITS DERIVATIVES AS POTENTIAL IMMUNOSTIMULANTS IN EXPERIMENTAL CANCER THERAPY.

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Arch Geschwulstforsch; 51(6):485-491 1981

The immunostimulant properties of 2-cyanoethyl urea (CEU) were studied in randomly bred male Wistar rats and ICR mice. Rats received CEU (varying doses) or ifosfamide (IF: 150 mg/kg body wt) iv. Mice were given CEU or IF po, iv, or ip. A single injection of 165 mg CEU/kg body wt increased WBC counts in rats up to 160% within 10 days, followed by a decline that was still above normal levels after 30 days. A single dose of IF produced a decrease in WBC count within 10 days which returned to normal after approx 20 days. CEU given in five doses of 165 mg/kg body wt significantly reduced the effects of IF and increased WBC count to 210% of initial values. Lymphocyte counts were raised 529%. A series of 20 CEU injections (165 mg/kg body wt) permanently raised WBC count 180% and lymphocyte count 560%. Plaque-forming cells in mouse spleens showed decreases following iv or po administration of CEU and in controls. Values for CEU-treated mice were always approx twice those for controls. As measured by footpad swelling CEU raised delayed type hypersensitivity in mice challenged with dinitrochlorobenzene. CEU showed low toxicity even at high doses. Results suggest the usefulness of CEU in clinical trials to improve immune response in human cancer patients. (19 Refs)

71. LYMPHOCYTE SUBPOPULATIONS AND RESPONSIVENESS IN RATS BEARING INTRACRANIAL TUMORS INDUCED BY AVIAN SARCOMA VIRUS.

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J Neurosurg; 55(4):554-559 1981

The mitogenic responsiveness of peripheral blood lymphocytes obtained from Fischer 344 rats inoculated with avian sarcoma virus was studied. In addition, quantitative alterations in lymphocyte subpopulations were determined in these animals. Only peripheral blood lymphocytes from rats bearing astrocytomas had significantly diminished responses to concanavalin A when compared to control responses. The percentage of lymphocyte subpopulations detected in either the peripheral blood or spleen of tumor-bearing rats did not differ from values obtained with control rats. However, rats bearing astrocytomas had a marked decrease in the absolute number of the various lymphocyte subpopulations as a result of lymphopenia. Neither the sarcoma-bearing rats nor the virus-inoculated rats that did not develop tumors exhibited this lymphopenia. In addition, sera from rats bearing astrocytomas diminished the concanavalin A reactivity of spleen cells obtained from normal rats. The results of this study established the avian sarcoma virus-induced rat astrocytoma model as a useful immunological parallel for the human disease. (Aut hor abstract) (22 Refs)

72. T CELL-MEDIATED IMMUNOSUPPRESSION AS AN OBSTACLE TO ADOPTIVE IMMUNOTHERAPY OF THE P815 MASTOCYTOMA AND ITS METASTASES.

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J Exp Med; 154(4):1033-1042 1981

T-cell immunosuppression in the presence of P815 mastocytoma and effects of passive transfer of sensitized T cells into the tumor host were examined in semisyngeneic male and female B6D2, CB6, DBA/2, and BALB/c mice. Growth of P815 mastocytoma evoked the generation of a state of T cell-mediated immunosuppression; it was possible to regress the P815 mastocytoma by passive transfer of tumor-sensitized T cells only if the tumors were growing in recipient mice that had been made T cell-deficient by thymectomy and gamma irradiation. Regression of the tumor was inhibited by an infusion of splenic cells from T cell-intact tumor-bearing donors. All T cell-deficient mice that received immune spleen cells 4 hr after removal of their day-6 primary tumors survived a 60-day observation period and remained free of palpable tumor metastases, while the recipients of normal spleens all died of tumor metastases with a median survival time of 19 days. Suppressor cells might inhibit the replication of passively transferred immune T cells, and thereby prevent these cells from reaching a number sufficient to cause tumor regression. Delaying the time of infusion of suppressor cells or infusing a smaller number allows enough time for the infused immune cells to expand in number in response to antigens supplied by the recipient's growing tumor. Results are similar to those previously obtained with the chemically induced Meth A fibrosarcoma. (7 Refs)

73. ADJUVANT EFFECT OF VITAMIN A PALMITATE AND ANALOGS ON CELL-MEDIATED IMMUNITY.

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JNCI; 67(5):1153-1156 1981

The sc route was used to study the adjuvant effect of vitamin A palmitate (VA) and the retinoids isotretinoin (Ro 4-3780), etretinate (Ro 10-9359), and motretinide (Ro 11-1430) on cell-mediated immunity to sheep RBC (SRBC) in outbred Mai:NIH(S) mice. The immune response was quantified by a sensitive assay procedure in which the antigen is injected intracutaneously into the pinna of the mouse, and the subsequent inflammatory swelling is measured with calipers. A single simultaneous injection of 150 ug VA enhanced cell-mediated immunity to SRBC as early as 3 days following immunization, and the enhancement persisted for at least 3 wk. Administered as a single injection 1 day or more before or after SRBC or as an ip injection, VA was not effective. Single injections of 100 ug isotretinoin and motretinide but not etretinate also enhanced the response. The effective agents possessed adjuvanticity comparable in magnitude to that of Bordetella pertussis vaccine. (Author abstract) (19 Refs)

74. EVIDENCE THAT THE SPONTANEOUS BLASTOGENESIS OF LYMPHOCYTES FROM BOVINE LEUKEMIA VIRUS-INFECTED CATTLE IS VIRAL ANTIGEN SPECIFIC.

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Infect Immun; 34(1):84-89 1981

Cattle lymphocytes cultures for 3 days were found to spontaneously incorporate thymidine (3STI). Under optimal conditions of culture, the median magnitude of 3STI activity in lymphocytes from bovine leukemia virus (BLV)-infected cattle was higher than that of BLV-free cattle, but the ranges of the values overlapped. However, the 3STI activity of most BLV-infected cattle was specifically inhibited by serum containing BLV antibodies, whereas the 3STI activity of BLV-free cattle was not. The 3STI inhibitor copurified with Ig, and its activity could be absorbed with BLV. Rabbit anti-BLV serum inhibited 3STI, but rabbit anti-BLV p25 did not. These results indicate that BLV infection induces or expands a BLV-specific lymphocyte population. Spontaneous blastogenesis may be indicative of an immune response which controls virus spread. (Author abstract) (27 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

75. THE EFFECT OF HUMAN FIBROBLAST INTERFERON (HUIFN-BETA) ON MALIGNANT TUMORS; IN VITRO EXPERIMENTS (MEETING ABSTRACT).

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Program and Abstracts of the 22nd Workshop on Selected Topics of the Japanese Society of Neuropathology held in Fukuoka, Japan, 9-11 May, 1981. The Japanese Society of Neuropathology, Kyoto 602, Japan, 136 pp., 1981.

Cultured brain tumor tissues obtained at the time of surgery were treated with HuIFN-beta or lymphocytes. A culture of a medulloblastoma obtained from a 6-yr-old boy was treated, beginning in 1 wk, with 0.7 x 10(1) IU or 0.7 x 10(3) IU of HuIFN-beta per ml three times a wk for 2 wk, and the growth rate was compared with that of the controls. The growth of the tissue in the petri dish containing 0.7 x 10(3) IU of HuIFN-beta per ml was inhibited 86%, as measured by colony area, as compared with the control, which agreed with the clinical effect on this patient. Morphological changes were seen in the cells given 7 x 10(3) IU of HuIFN-beta per ml; the cells generally became long and thin and some had a differentiated astrocyte-like appearance with long projections. The growth of the glioma cell line was not inhibited by the addition of 0.7 x 10(3) IU of HuIFN-beta per ml. The growth of malignant astrocytoma tissue from a 29-yr-old male patient was inhibited by 12%, 65%, and 85% compared to the control when the autochthonous peripheral lymphocytes alone, HuIFN-beta (3 x 10(3) IU/ml) alone, and lymphotes + HuIFN-beta, respectively, were added. The 51Cr release assay using K562 cells as the target cells showed cytotoxicity of 4.7% for HuIFN-beta alone and 40% for the HuIFM-beta + lymphocytes. Cytotoxicity was about 30% when the lymphocytes were incubated with HuIFN-beta for 2 hr, washed and then applied to the target cells. These results indicate that HuIFN-beta has a direct effect on the tumor and an effect mediated by lymphocytes, the greatest tumor growth inhibition or cytocidal effect being produced when HuIFN-beta and the lymphocytes were added together. (no Refs) (In JPN)

76. SUPPRESSIVE EFFECT OF SUPERNATANT OF MIXED LYMPHOCYTE TUMOR CELL CULTURES (MLTC) ON THE GROWTH OF HUMAN GASTRIC CARCINOMA TRANSPLANTED IN NUDE MICE.

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Nippon Geka Gakkai Zasshi; 82(4):305-315 1981

Human gastric carcinomas, KSt-1 and St-15, which had been maintained in nude mice, were used as human tumors, and the effect of human lymphocytes on the tumor growth was examined. The growth of St-15 in nude mice was temporarily inhibited by injection of human lymphocytes sensitized in MLTC but not by nonsensitized ones. Injection of supernatant of MLTC to tumor-bearing nude mice suppressed the tumor growth markedly. Spleen cells of nude mice injected with MLTC-supernatant showed significantly increased natural killer (NK) activity, as determined by 51Cr-release assay on YAC, and increased macrophage activity, as determined by inhibition of 3H-thymidine uptake by H-2 syngeneic P-815.

These results indicate that human lymphocytes sensitized to tumor may recognize allogenic human lymphocyte antigen on tumor cells and temporarily inhibit the tumor growth, and that MLTC-supernatant activates NK cells as well as macrophages in tumor-bearing nude mice and these activated cells prevent the tumor growth. (39 Refs) (In JPN)

77. MACROPHAGE AND T LYMPHOCYTE CONTENT OF TUMORS IN MICE TREATED WITH PROPIONI BACTERIUM.

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Dept. Radiotherapy, Postgraduate Center, Sch. Medicine, Warsaw, Poland
Oncology; 38(6):334-339 1981

Macrophage and T lymphocyte content of sarcoma tumors in mice treated with Propionibacterium granulosum (PG) by different routes was investigated and compared with the effectiveness of the therapy. Two different methods for tumor macrophage detection, the Fc receptor analysis and phagocytic properties, were employed. Indirect fluorescent staining of theta-antigen on lymphocytes was used to evaluate the proportion of tumor T cells. Systemic treatment with PG appeared to be effective if given soon after tumor implantation; however, this route of administration failed to affect the tumor growth if given when the tumor was already advanced. The therapeutic efficiency of intralesional PG injection was almost as effective as early systemic treatment. We obtained evidence indicating that effectiveness of PG therapy was associated with an increase of the macrophage and T cell content of tumors. (Author abstract) (31 Refs)

78. HELPER CELLS ACTIVE IN THE GENERATION OF CYTOTOXICITY TO A SYNGENEIC TUMOR.

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J Immunol; 127(4):1394-1397 1981

We have examined a population of thymic lymphocytes that augment the generation in vitro of specific cytotoxic T cells against P815.X2, a syngeneic tumor in DBA/2 mice. These helper cells are evident in the thymus of DBA/2 mice 5 to 7 days after sc injection of live P815 cells. They are Thy-1 positive, resistant to gamma radiation, antigen specific, and appear to exert their influence most effectively when added at the beginning of the culture. (Author abstract) (40 Refs)

79. EFFECTS OF GAMMA-IRRADIATION ON LYMPHOCYTE SUBPOPULATIONS PARTICIPATING IN THE DEVELOPMENT OF THE CYTOTOXIC T LYMPHOCYTE RESPONSE.

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J Immunol; 127(4):1485-1489 1981

Differences in radiosensitivity among lymphocyte subpopulations involved in generating allogeneic cytotoxic T lymphocyte (CTL) responses were studied. Gamma irradiated splenic lymphocytes from C57BL/6 mice (B6, H-2b) were stimulated in vitro with DBA/2 (H-2d) spleen cells or the DBA/2 mastocytoma, P815. Limiting dilution analysis indicated that the cytotoxic T lymphocyte effector cells (CTLe) for either antigen arose from the same pool of cytotoxic T lymphocyte precursors (CTLp), and that the D37 value of the B6 anti-H-2d CTLp was approx 165 R. In mixed lymphocyte cultures, however, differential effects of irradiation were seen between the two antigens in the ability of irradiated responder B6 spleen cells to generate CTLe. For induction of cytotoxic activity against DBA/2 splenocytes, the CTLp was the most radiosensitive component of the response, whereas the generation of a cytotoxic response against P815 was limited by the radiosensitivity of an Lyt-1 T helper cell (D37 approx 85 R). The radiosensitive Lyt-1 cell could be replaced by mixed lymphocyte reaction supernatants or semipurified interleukin 2 (IL-2) from Con A-stimulated murine spleen cells. The requirement of B6 anti-H-2d CTLp for a radiosensitive accessory cell in the CTL response against P815, in contrast with their activation by DBA/2 splenocytes, may center on the fact that the tumor cells do not possess Ia antigens. (Author abstract) (43 Refs)

80. EPIDERMAL CELL (KERATINOCYTE)-DERIVED THYMOCYTE-ACTIVATING FACTOR (ETAF).

Luger TA, Stadler BM, Katz SI, Oppenheim JJ
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J Immunol; 127(4):1493-1498 1981

In order to determine whether keratinocytes play a role in the modulation of the immune response, we investigated the murine keratinocyte cell line Pam 212. In culture these cells generate a substance with a biologic activity that greatly enhances phytohemagglutinin-induced thymocyte proliferation. We have, therefore, called this substance epidermal cell thymocyte-activating factor (ETAF). This keratinocyte-derived supernatant activity is mainly produced at the onset of the logarithmic growth phase and is directly mitogenic for murine thymocytes. Although ETAF by itself exhibits no T cell growth factor activity, ETAF enhances interleukin 2 production by mitogen-stimulated murine spleen cells. Murine ETAF is not genetically restricted and lacks species specificity since it decreases lectin-induced proliferation of human peripheral blood lymphocytes (as well as murine spleen cells) and also enhances the production of human interleukin 2. The factor has a mol wt between 15,000 and 25,000 as determined by gel filtration and elutes as a single peak from anion exchange chromatography columns. The activity is maintained mainly at alkaline pH and is rapidly destroyed at temperatures above 60 C. These observations suggest that epidermal cells may interact with the immune system by elaborating nonspecific factors that modulate lymphocyte proliferation and augment lymphokine production. (Author abstract) (41 Refs)

81. FORMATION OF IGE-BINDING FACTORS BY RAT T LYMPHOCYTES. I. INDUCTION OF IGE-BINDING FACTORS BY POLY I:C AND INTERFERON.

Yodoi J, Hirashima M, Bloom BR, Ishizaka K
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J Immunol; 127(4):1579-1585 1981

Rat serum obtained 8 to 18 hr after an ip injection of poly I:C contained IgE-binding factors, which can be detected by the inhibition of rosette formation of FcepsilonR(+) cells with IgE-coated RBC. Incubation of normal rat spleen cells with 1 ug/ml poly I:C resulted in the formation of IgE-binding factors. Approx one-half of the IgE-binding factors in the culture supernatant were IgE-potentiating factors, which have affinity for concanavalin A (Con A), whereas the remaining half of the factors were IgE-suppressive factors with no affinity for the lectin. Culture supernatants of poly I:C-stimulated spleen cells as well as the serum of poly I:C treated rats contained not only

IgE-binding factors but also soluble factors that induce normal lymphocytes to form IgE-binding factors. It was found that poly I:C-stimulated splenic adherent cells and peritoneal macrophages formed soluble factors, which in turn induced T lymphocytes to express FcepsilonR and to form IgE-binding factors. The inducers derived from poly I:C-stimulated cells failed to augment the expression of FcepsilonR on B cells. The soluble factors could induce the formation of both IgE-potentiating factors and IgE-suppressive factors. Upon incubation with the inducers, 10 ug/ml Con A-activated cells formed IgE-potentiating factors; 1 ug/ml Con A-activated cells formed IgE-suppressive factors. The inducers had affinity for polyuridylic acid and blue dextran Sepharose, and could be recovered from the beads by elution with 1 M NaCl. It was also found that supernatant of mouse spleen cells co-cultured with virus-infected HeLa cells induced normal rat lymphocytes to form IgE-binding factors. The inducers in the culture supernatants were neutralized by a minute dose of antibodies specific for mouse Type I interferon, indicating that mouse interferon can induce the formation of IgE-binding factors. (Author abstract) (40 Refs)

82. RECOGNITION OF MOPC-460 VARIABLE REGION DETERMINANTS BY POLYCLONALLY DISTRIBUTED TRIGGERING RECEPTORS ON B LYMPHOCYTES.

Primi D, Juy D, Le Guern C, Sanchez P, Cazenave PA
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J Immunol; 127(4):1714-1718 1981

Purified M460 protein-induced untreated and anti-Thy 1.2 and complement-treated murine spleen cells to proliferate and differentiate in vitro. Fc receptor complexing was not responsible for the phenomenon, since M460 Fab fragments retained the B cell triggering activity. Activation was inhibitable by the addition of DNP-glycine to cultures and could also be detected by using spleen cells from various strains of mice, including the C3H/HeJ, which is genetically nonresponding to LPS. Hybrid molecules were constructed between the M460 proteins and the products of two myelomas that do not activate B cells, namely, X25 and X24. The only hybrid molecules that retained triggering activity were (L460-HX25)2. Interestingly, the same molecule was also the only one recognized by an anti-M460 monoclonal antibody (F6(51)) that has been previously shown to induce B cells to proliferate and differentiate. The data suggest the existence on B lymphocytes of a network of polyclonally distributed mitogen receptors that share determinants cross-reacting with Ig idiotypes. (Author abstract) (21 Refs)

83. ENHANCEMENT OF MACROPHAGE-INDUCED CYTOTOXICITY BY PHORBOL ESTER TUMOR PROMOTERS.

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Cancer Res; 41(11,part1):4523-4528 1981

The potent tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), markedly enhanced the ability of mouse peritoneal macrophages to inhibit the growth of L5178Y tumor cells as measured b y growth in agar. Three populations of macrophages, resident, divinylether maleic anhydride copolymer, and thioglycollate-recruited, were used. In general TPA reduced both the cocultivation time and the number of macrophages required to induce cytotoxicity in all three macrophage types. With divinylether maleic anhydride copolymer macrophages, TPA enhanced cytotoxicity in a dose-dependent manner in the concentration range of 1.7 to 170 nM at macrophage:tumor cell ratios of 10:1 and 1:1. For reasons that were not apparent, inhibition of cytotoxicity was found at higher cell ratios. With both thioglycollate-elicited and resident macrophages, TPA (170 nM) enhanced cytotoxicity at all ratios tested. Even 1:1 ratios of macrophages:tumor cells, which were not cytotoxic alone, inhibited cell viability by 50% to 60% in the presence of TPA. A correlation was found between the biological activity of related macrocyclic diterpenes and their ability to enhance macrophage-mediated cytotoxicity. Thus, mezerein and phorbol didecanoate enhanced macrophage cytotoxicity, while the biologically inactive analogs, phorbol, 4-O-methyl-12-O-tetradecanoylphorbol-13-acetate, and 4-alpha-phorbol-12,13-didecanoate were without effect in this assay. Cytotoxicity towards untransformed BALB/c/3T3 cells was also demonstrated using a liquid cloning assay. These target cells were much less sensitive to growth inhibition by the macrophages than were the L5178Y cells. A 50% decrease in survival occurred only after 48 hr incubation and required macrophage:target cell ratios of 100:1. The addition of 170 nM TPA led to a dramatic enhancement of cytotoxicity in these cells at macrophage:target cell ratios of 10:1 and 1:1. The results observed with the phorbol esters in the present studies are compatible with other evidence that these compounds can modulate a variety of macrophage functions. (Author abstract) (50 Refs)

84. STIMULATION OF HUMAN GAMMA INTERFERON PRODUCTION BY DITERPENE ESTERS.

Yip YK, Pang RH, Oppenheim JD, Nachbar MS, Henriksen D, Zerebeckyj-Eckhardt I, Vilcek J

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Infect Immun; 34(1):131-139 1981

The diterpene ester 12-O-tetradecanoylphorbol-13-acetate (TPA) and several structurally related compounds were tested for their ability to stimulate interferon (IFN) production in primary cultures of human WBC. In cultures of Ficoll-Hypaque-purified mononuclear cells, TPA treatment alone induced only low levels of IFN, but TPA pretreatment of cells caused significant enhancement of IFN yields produced with phytohemagglutinin or several other T cell mitogens. In cultures of unprocessed cells derived from plateletpheresis residues or buffy coats, TPA treatment alone induced high levels of IFN and costimulation with TPA and phytohemagglutinin produced some further enhancement of IFN production. Phorbol 12,13-dibutyrate wa s comparable to TPA in its ability to enhance phytohemagglutinin-induced IFN production. Several other phorbol ester analogs were also active, but max stimulation occurred only at higher drug concentrations. Mezerein, a structurally related diterpene ester, was at least as active as TPA in stimulating IFN production in either Ficoll-Hypaque-purified or unprocessed cells. IFN produced after stimulation with TPA or mezerein, singly or in combination with phytohemagglutinin, had several properties characteristic of IFN-gamma, eg, it was largely inactivated by dialysis at pH 2, or after exposure to sodium dodecyl sulfate, whereas it was not neutralized by antibody to IFN-alpha and IFN-beta. The stimulatory effect of diterpene esters has proved helpful in producing IFN-gamma for physicochemical analysis and other studies. (Author abstract) (39 Refs)

85. CYTOTOXIC EFFECT OF ONION EXTRACT ON MOUSE FIBROSARCOMA 180 A CELLS.

Nerkar DP, Chander R, Bandekar JR, Tewari GM, Bandyopadhyay C
Biochemistry and Food Technology Div., Bhabha Atomic Res. Centre, Bombay 400 085, India
Indian J Exp Biol; 19(7):598-600 1981

The antitumor activities of onion extract (OE) and lacrimatory factor (LF) were investigated in mouse fibrosarcoma 180 cells (MFS-1). Cytotoxicity of OE was related to its concentration and time of incubation with ascites cells; cytotoxic effect as a function of concentration was nonlinear. Swiss male mice injected with cells which were treated with 150-200 ug OE for 3 hr did not develop tumors, while those treated with 50-100 ug OE did form ascites tumor. OE was cytotoxic to spleen cells and macrophages at doses of 200 ug/ml or more, while OE at doses as high as 450 mg/ml were nontoxic in vivo. When mice were transplanted with MFS-180 cells followed by three or four consecutive injections of 45 mg/kg/mouse starting at 0, 1, 2 or 4 days after transplantation, survival time of mice given OE on day 0 was extended over that of controls with only marginal effect in the other groups. LF appeared to be more cytotoxic than OE to MFS-180 cells. However, no significant prolongation of survival time of mice given LF was noted over controls. (12 Refs)

86. INTERLEUKIN 2 PRODUCTION BY ALLOANTIGEN (H-2) ACTIVATED T CELLS.

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Aust J Exp Biol Med Sci; 59(4):413-426 1981

H-2 alloantigen-activated T cells release Interleukin 2 in response to a secondary stimulus by either Concanavalin A or alloantigen. No detectable lymphokine is released in the absence of secondary stimulation and, in the case of alloantigen restimulation, lymphokine release is antigen-specific. Once formed, however, the lymphokine shows no antigen specificity in its action. Like the precursor of the cytotoxic T cell, the precursor of the Interleukin 2-producing T cell requires two signals for its activation; alloantigen and a source of costimulator activity. Once activated, T cells will release lymphokine in response to alloantigen alone. (Author abstract) (18 Refs)

87. THE DUAL INTERACTION OF PROSTAGLANDIN E2 (PGE2) AND INTERFERON (IFN) ON NK LYTIC ACTIVATION: ENHANCED CAPACITY OF EFFECTOR-TARGET LYTIC INTERACTIONS (RECYCLING) AND BLOCKAGE OF PRE-NK CELL RECRUITMENT.

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J Immunol; 127(4):1424-1428 1981

In this study we addressed the question of whether the known NK activators prostaglandin E2 (PGE2) and interferon (IFN) can synergistically activate NK lysis and whether they potentiate the same or different subsets of NK cells. We demonstrated that the activation of NK lysis can be enhanced as well as blocked by the interaction of these two activators. The enhancement of activation was not due to recruitment of separate subsets of pre-NK cells, but rather the synergistic enhancement of the recycling capabilities of the same set of NK cells. There was a temporal relationship to this enhancement. That is, if PGE2 was added during cellular processing required for full expression of NK activation induced by IFN, pre-NK lytic potential was inhibited. If, on the other hand, PGE2 is added after completion of full expression of the IFN-induced activated lytic process, there is enhancement of recycling capabilities of the same number of NK cells. (Author abstract) (18 Refs)

88. COMPARISON OF ANTITUMOR EFFECT OF TWO DISTINCT IMMUNOPOTENTIATING AGENTS ON A SYNGENEIC SOLID TUMOR TRANSPLANTED TO NU/NU OR NU/+ MICE.

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Dept. Surgery, Sch. Medicine, Keio Univ., Shinjuku-ku, Tokyo 160, Japan
Nippon Ganka Gakkai Zasshi; 82(4):324-336 1981

The antitumor effect of two immunopotentiating agents, OK-432, a streptococcal preparation, and levamisole was compared in several aspects. A fibrosarcoma, KKN-1, which was induced in a BALB/c mouse by 3-methylcholanthrene and had been maintained by serial transplantations in BALB/c nu/+ or nu/nu mice, was used as a tumor, and syngeneic nu/nu or nu/+ mice were used as tumor hosts. OK-432 at a daily dose of 50 KE/kg or levamisole at a daily dose of 1 mg/kg was administered ip to mice. Neither drug showed any effect on the growth of KKN-1 transplanted to nu/nu mice, whereas both drugs inhibited the tumor growth in nu/+ mice. These results indicate the importance of T cell function of the mice in the antitumor effect of both drugs. This was also suggested by the results that impaired blastogenic response to phytohemagglutinin or concanavalin A of spleen cells from tumor-bearing nu/+ mice significantly recove red by treatment of the mice with either drug. Winn's tumor neutralizing assay also showed antitumor activity of spleen cells of tumor-bearing nu/+ mice treated with OK-432. Administration of either drug daily from 1 day to 5 days after tumor transplantation showed pronounced antitumor effect, whereas the same dose given from 6 to 10 days after the transplantation showed reduced effect. OK-432, but not levamisole was effective even when the drug was given daily for 5 days before the tumor transplantation. Combined immunochemotherapy using OK-432 and mitomycin C (MMC) showed a synergistic effect when OK-432 was administered after MMC, while no additive effect was obtained when the sequence of the administration of the two drugs was reversed. Additive effect was observed when levamisole was combined with MMC, regardless of the sequence of the administration. (47 Refs) (In JPN)

89. ANTITUMOR ACTIVITY OF HOT WATER EXTRACT OF DANDELION, TARAXACUM OFFICINALE - CORRELATION BETWEEN ANTITUMOR ACTIVITY AND TIMING OF ADMINISTRATION.

Baba K, Abe S, Mizuno D
Central Res. Lab., Sankyo Co. Ltd., Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140, Japan
Yakugaku Zasshi; 101(6):538-543 1981

Antitumor effects of a non-dialyzable hot water extract, Tof-CFr, that was isolated from dandelions (Taraxacum officinale), were investigated with ICR, ddY, and C3H/Hef mice bearing Ehrlich and MM46 ascites tumors or sarcoma 180 tumors. The antitumor effects of the Tof-CFr were compared with those produced by administration of lentinan and yeast mannan. Following sc transplantation of tumor cells in the mice, the Tof-CFr, lentinan, and yeast mannan were administered daily on days 1-10, or on days 11-20, or every other day on days 2-20 in doses of 20-60 mg/kg, 1.7 mg/kg, and 60 mg/kg, respectively.

Day 35 after transplantation, the tumors were resected and the tumor wt was determined. The Tof-CFr had antitumor effects on the allogeneic ddY-Ehrlich tumor system and on the syngeneic C3H/Hef-MM46 tumor system when administered days 11-20 or 2-20 but not if administered days 1-10. For the lentinan and the yeast mannan, timing of administration was important only for the ddY-Ehrlich system. The Tof-CFr showed cytolytic activation of macrophages in antibody-dependent macrophage mediated cytolysis and enhanced antitumor delayed hypersensitivity reactions in the ddY-Ehrlich and C3H/Hef-MM46 systems, suggesting a tumor growth-inhibiting action similar to that of lentinan. (10 Refs) (In JPN)

90. IN VIVO IMMUNOSTIMULATING PROPERTIES OF TWO RETINOIDS: RO 10-9359 AND RO 13-6298.

Hercend T, Bruley-Rosset M, Florentin I, Mathe G
Institut de Cancerologie et d'Immunogenetique, Hopital Paul-Brousse, F-94800 Villejuif, France
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

The effects of Ro 10-9359 and Ro 13-6298 on various aspects of immune cell activation and immune system responsiveness to certain challenges were examined in several strains of mice. The incidence and histological type of tumors in both treated and untreated mice were recorded and compared in mice that died or were sacrificed for other testing; Ro 10-9359 appeared to significantly decrease or delay the appearance of tumors. (16 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

91. TUMOR REGRESSION BY A COMBINATION OF THE CODE FACTOR (CF) OF BCG AND THE ENDOTOXIC GLYCOLIPID (GL) OF SALMONELLA (MEETING ABSTRACT).

Sasaki J, Fukushi F
Dept. Bacteriology, Hirosaki Univ., Faculty Medicine, Hirosaki-shi, Aomori Prefec. 036, Japan
Kekkaku; 56(4):247 1981

The CF was extracted from BCG by the Noll and Bloch method, and the GL either from the whole body or cell wall of peptose-free Salmonella minnesota 1167-R595 (Re mutant). Five to 7 days after ascites serial line 10 hepatocarcinoma was transplanted id into inbred line, strain 2 guinea pigs, the GL + CF was injected into the tumor in the form of oil-in-water, and the regression in the area of the tumor and the number of animals cured were compared with those of the control animals. The tumors regressed 40% when the GL obtained from the whole bacterial body was combined with CF, but there was 71% regression when the GL obtained from the cell wall fraction was combined with CF. Both of these GLs were toxic as judged by the limulus test at the low dose of 2 x 10(-5) ug/ml, but the toxicity was reduced, requiring 2 x 10(-1) ug/ml, when the GL was decomposed by 0.1 N NaOH, although the regression rate was still 67%. When all the ester-bound lipid A was liberated by decomposition with 2% alkaline hydroxylamine, 2% NH2OH in 4% NaOH in ethanol, the limulus activity was weakened to show toxicity only at 25 ug/ml or higher, although the tumors regressed by 75%. When GL was used alone there was hardly any tumor regression, with the tumor-bearing guinea pigs all dying at about day 40. Tumor specific activity and delayed-type hypersensitivity reactions were induced in the skin of the animals totally cured by GL + CF combined therapy. Together with the findings obtained on the macrophage-lymphocyte change in tumor-bearing animals, and from in vitro experiments with tumor cells, the tumor regression obtained by this method is considered to be based on systemic immunity. (no Refs) (In JPN)

92. CHARACTERIZATION OF THE RECOGNITION OF TARGET CELLS SENSITIVE OR RESISTANT TO CYTOLYSIS BY ACTIVATED RAT PERITONEAL MACROPHAGES.

Hamilton TA, Fishman M
Div. Immunology, St. Jude Children's Res. Hosp., Memphis, TN, 38101
J Immunol; 127(4):1702-1706 1981

The interaction between tumoricidal rat peritoneal exudate macrophages and normal or neoplastic target cells has been examined both with respect to the sensitivity of the target cells to macrophage-mediated cytolysis and the ability of such targets to compete with one another for the lytic activity of macrophages. The results demonstrate that, in confirmation of earlier work from other laboratories, target cells are either sensitive or largely resistant to lysis, and such sensitivity correlates well with the neoplastic phenotype of the target cell. However, in target cell competition experiments all cultured cells as well as Con A-stimulated splenocytes and freshly isolated thymocytes exhibit the capacity to block cytolysis of sensitive indicator targets. In contrast, freshly prepared non-mitogen-stimulated splenic or lymph node lymphocytes are completely devoid of competitive activity. These results show that macrophages can recognize and interact with both normal and tumorigenic cells and that such target recognition can be distinguished from target cytolysis. Furthermore, the evidence suggests that at least one target cell feature that correlates with recognition is cell cycle traverse. (Author abstract) (22 Refs)

93. THE IN SITU INDUCTION OF TUMORICIDAL ACTIVITY IN ALVEOLAR MACROPHAGES BY LIPOSOMES CONTAINING MURAMYL DIPEPTIDE IS A THYMUS-INDEPENDENT PROCESS.

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J Immunol; 127(4):1719-1720 1981

The ability of rat alveolar macrophage (AM) activation to occur in recipients that are unable to reject immunologically a syngeneic tumor was studied in three groups of mice. Group I, C3H/HeN mice were UV-irradiated for 8 wk. Group II mice, were nonspecifically immunosuppressed by thymectomy at 4 wk of age and by whole-body irradiation 1 wk later. Group III consisted of congenitally athymic NIH/S nude mice with well-characterized immune deficiency. In all experiments, mice were injected iv with multilamellar vesicles. AMs were injected iv. Macrophage-mediated cytotoxicity in vitro was measured by release of radioactivity from a 125I-iodo-deoxyuridine prelabeled B16 melanoma (syngeneic to C57BL mouse), UV-2237 fibrosarcoma (syngeneic to C3H/HeN mouse), or nontumorigenic fibroblast cell line (syngeneic to NIH/S mouse). AMs harvested from all groups of mice became tumoricidal in response to liposome-encapsulated muramyl dipeptide (MDP). Both the B16 melanoma and the UV-2237 fibrosarcoma cells were lysed by AMs harvested from the various recipients but the nontumorigenic fibroblasts were unharmed. The iv injections of liposomes containing Hanks' balanced salt soln and suspended in free MDP failed to render AMs tumoricida These results indicate d that the liposome-entrapped MDP was responsible for the activation of AMs to become cytotoxic. (23 Refs)

94. SENSITIVITY OF ACUTE MYELOID LEUKAEMIA CELLS TO COLONY STIMULATING ACTIVITY: RELATION TO RESPONSE TO CHEMOTHERAPY.

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Br J Haematol; 49(2):259-267 1981

Agar cultures of acute myeloid leukemia (AML) cells were used to determine the sensitivity of AML clone forming cells to the specific regulator granulocyte-macrophage colony stimulating activity (CSA). The mean CSA threshold (amount of CSA required to stimulate 0.5 of the clone forming cells) of 27 different AML cell samples varied from normal to an approx nine-fold increase in CSA requirement. The degree of sensitivity to CSA at presentation was found to be closely correlated to the response to induction chemotherapy in 15 patients. There was a highly significant correlation (p less than 0.001) between the mean CSA threshold and the number of courses of chemotherapy required to induce remission. Also, an increased mean CSA threshold at presentation was associated with a significantly slower decline of marrow blasts following the first course of chemotherapy and a reduced remission rate. Sensitivity to CSA was closely related to the clone size achieved in maximally stimulated cultures of AML cells and this in turn also related to the remission rate and ease with which remission was achieved (presentation marrows, 39 patients). Possible reasons for the linking of these two functional properties of AML cells and their relation to response to chemotherapy will be discussed. (Author abstract) (12 Refs)

95. MURINE MACROPHAGE INTERFERONS.

Mentkevich LM, Churbakova EV
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Vopr Virusol; (4):410-414 1981

Interferon (IF) production in peritoneal macrophages of C57BL/6 mice was studied. The peritoneal macrophages were shown to produce IF type I and immune IF in response to virus or phytohemagglutinin used as inducers. Production of a given type of IF depended upon the method of induction. The cultures of peritoneal macrophages did not contain spontaneous IF. (22 Refs) (In RUS)

96. EFFECT OF MACROPHAGES ON THE GROWTH OF SYN- AND XENOGENEIC TUMORS.

Lapis K, Kopper L, Timar J, Tran-van-Hanh, Hegedus C
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Arch Geschwulstforsch; 51(6):475-479 1981

Data from several studies on the effect of macrophages in syngeneic and xenogeneic tumor systems are presented. Human colorectal tumors were transplanted into thymectomized, irradiated and bone-marrow reconstituted mice (syngeneic system). During serial passages tumor takes ranged between 50-80%. Blocking the activity of macrophages by pretreatment with carrageenan (CAR) increased tumor takes, shortened time for tumors to reach palpable size, without subsequent change in their growth rate or structure. In a xenogeneic system, CAR had a tumor growth enhancing effect in mice with metastatic Lewis lung tumor (LLT). After im LLT implantation, nodules in lung were countable in about 3 wk. When CAR was given before or after tumor implantation, tumor wt and number of metastases increased, while survival time was decreased. In mice with LLT cells injected intrasplenically, iv CAR (1 mg/mouse) caused lysosomal damage in Kuppfer cells as had been seen in peritoneal macrophages. The role of macrophages in the tumor-host relationship was studied by treating the host with peritoneal macrophages. Iv injection of 5 x 10(6) adherent peritoneal cells two days after im transplantation of LLT or one day after removal of primary tumor (day 10 after transplantation) led to significant decrease of lung metastases, and reversal of thymus and spleen wt. Iv injection of xenogeneic tumor-bearing mice with peritoneal macrophages also produced a delay in tumor growth. These studies suggest that CAR produces its effect by attacking macrophages. Studies with LLT indicate macrophages markedly influence tumor progression, even in hosts with damaged T cell populations. (13 Refs)

97. AUTORADIOGRAPHIC DISTRIBUTION OF HEMATOPORPHYRIN DERIVATIVE IN NORMAL AND TUMOR TISSUE OF THE MOUSE.

Bugelski PJ, Porter CW, Dougherty TJ
(c/o Dougherty) Div. Radiation Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Res; 41(11,part1):4606-4612 1981

The distribution of isotopically labeled hematoporphyrin derivative (HPD) has been studied in mice bearing the spontaneous mammary tumor (fast growing). In stomach, liver, spleen, and pancreas, 3 hr after ip injection of [3H]HPD, grains were uniformly distributed over the tissue sections. After 24 hr, the grain density overlying parenchymatous areas of these tissues was lower than that over the stromal or reticuloendothelial areas. In the spontaneous mammary tumor (fast growing), higher grain densities were seen over pseudocapsule, stromal septa, and necrotic areas at 3, 6, 12, 24, and 48 hr after injection. At 168 hr postinjection, only isolated stromal cells, presumably macrophages, showed high grain densities. From the temporal changes observed in the distributions of HPD in normal tissues and the relative stability of the distribution seen in the spontaneous mammary tumor (fast growing), we speculate that tissue factors such as vascular permeability, lack of an adequate lymphatic drainage, and nonspecific binding of serum proteins to stromal elements may be responsible for or contribute to the preferential uptake and/or retention of HPD observed in both human and animal tumors. (Author abstract) (32 Refs)

98. STUDY OF MONOCYTE FUNCTION IN PATIENTS WITH CERVICAL CANCER BY USING T-LYMPHOCYTE MONOCYTE INTERACTION IN RESPONSE TO PHYTOHEMAGGLUTININ (PHA).

Umesaki N, Nakade J, Nakamori H, Sako H, Lee T, Sugawa T
Dept. Obstetrics and Gynecology, Osaka City Univ., Medical Sch., Abeno-ku, Osaka 545, Japan
Nippon Sanka Fujinka Gakkai Zasshi; 33(5):664-670 1981

Responding lymphocytes were graded as T cells obtained from healthy volunteers and monocytes were added to the T cells. Monocyte function in this study was as follows: PHA response to T cells and monocytes over PHA response to T cells. In this study, monocytes were allogenic to T cells. At first, the influence of monocytes on allogenic T cells was studied but it was found to be negligible. The ratio of monocytes and T cells was 1:1. The concentration of PHA was 20 ug/ml. Finally, the monocyte function of patients with cervical cancer was studied. It was increased at the stage of carcinoma in situ and then gradually decreased. At the advanced stage, it was significantly decreased in comparison with that of healthy volunteers. (16 Refs) (In JPN)

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY

99. INTERFERON ENHANCES THE ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC) OF HUMAN POLYMORPHONUCLEAR LEUKOCYTES.

Hokland P, Berg K
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J Immunol; 127(4):1585-1588 1981

Polymorphonuclear WBC (PMN) from healthy volunteers were tested for ADCC activity against both RBC and tumor targets with and without the addition of human WBC interferon (IFN). It was demonstrated that IFN within 30 to 60 min enhanced the reaction in a dose-dependent manner with minimal IFN doses ranging from 1 to 100 units. Formal proof that the augmenting agent was IFN was obtained by using pure IFN proteins in combination with both mock-IFN preparations, which showed no enhancing activity, and anti-IFN antisera, which inhibited the action of the completely purified IFN protein. In the light of data demonstrating that the IFN effect was most pronounced when the IgG antibodies in the ADCC reaction were present in suboptimal amounts, it is hypothesized that IFN may play a special role in the early nonspecific immune response against non-self antigens. (Author abstract) (14 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

100. CELL HYBRIDIZATION: A MONOCLONAL MARKER AS A DIAGNOSTIC AID IN HEMATOLOGY AND ONCOLOGY.

Tilz GP, Beverley P, Becker H, Lanzer G, Sedlmayr P
Medizinische Universitatsklinik, Auenbruggerplatz 15, A-8036 Gratz, Austria
Acta Med Austriaca; 8(3):85-87 1981

A monoclonal marker for hematologic and oncologic purposes was developed. Male BALB/c mice were immunized sc with 4.5 x 10(6) human lymphocytes and boosted ip at monthly intervals with 2-5 x 10(6) of the same type cells. Four days after the last booster dose, spleen cells were obtained from the mice and fused with NS-1 plasmacytoma cells. Polyethylene glycol (40% soln) was used as a fusing agent. Cells were grown on selective heterophilic antibody titer medium. Cells were selected and cloned on the basis of antibody production. Clones were tested for antibody activity against infantile thymus, lymph node, tonsil, bone marrow, and various solid tumor tissues, as well as leukemic and erythroleukemic cells. One IgG 1-producing clone was identified that reacted with lymphoid cells, band cells, polymorphs, eosinophils, and macrophages. The clone did not react with erythropoietic cells or with undifferentiated carcinoma cells. It was designated H Le D 1. Use of this clone allows differential diagnosis of undifferentiated carcinomas and lymphoid malignancies. (10 Refs) (In GER)

101. AN AUTOANTIBODY REACTIVE WITH NUCLEI OF POLYMORPHONUCLEAR NEUTROPHILS: A CELL DIFFERENTIATION MARKER.

Whittingham S, Morstyn G, Wilson JW, Vadas MA
Clinical Res. Unit., Walter and Eliza Hall Inst. of Medical Res., Royal Melbourne Hosp., Victoria 3050, Australia
Blood; 58(4):768-771 1981

An autoantibody that reacted with nuclei of polymorphonuclear neutrophils (PMN) was detected at titers of greater than 10 in sera of 25 of 50 patients with rheumatoid arthritis and 36 of 50 with autoimmune chronic active hepatitis but in none of 160 controls comprising 24 patients with alcoholic cirrhosis, 36 with multiple myeloma, and 100 healthy subjects. Through the use of enriched populations of hemopoietic cells, this antibody was shown to be cell-specific, reacting only with the nucleus of the mature neutrophil. It was unreactive with nuclei of progenitor cells in the myeloid series and with nuclei of eosinophils, monocytes, lymphocytes, and thymocytes. It reacted with a determinant that appeared to be a differentiation antigen. This cell-specific autoantibody may prove to be of value in analytical studies of granulocyte maturation. (Author abstract) (20 Refs)

CMI METHODOLOGY

102. LYMPHOCYTE CYTOTOXICITY AGAINST AUTOLOGOUS BLADDER TUMOR CELLS IN HUMANS, INVESTIGATED BY USE OF A CHROMIUM-51 RELEASE ASSAY.

Jacobsen F
Univ. Inst. Pathology, Aarhus Amtssygehus, DK-8000 Aarhus C, Denmark
Acta Pathol Microbiol Scand [C]; 89(3):175-180 1981

A technique for isolation of a single cell suspension of viable tumor cells from bladder tumor biopsies is described. By application of the tumor cells as targets in a 51chromium release assay, the cytotoxicity of autologous lymphocytes was measured in 38 patients with transitional-cell tumors of the urinary bladder. The lymphocyte-mediated cytotoxicity was evaluated in relation to the histological grade and clinical stage of the bladder tumors. No significant correlations were found between the autologous cytotoxicity and the grade or stage of the bladder tumors. (Author abstract) (23 Refs)

103. IN VITRO PRODUCTION OF HUMAN ANTIBODY TO A TUMOUR-ASSOCIATED FOETAL ANTIGEN.

Irie RF, Jones PC, Morton DL, Sidell N
Div. Oncology, Univ. California Sch. Medicine, 54-140 CHS, Los Angeles, CA, 90024
Br J Cancer; 44(2):262-266 1981

After the establishment of lymphoblastoid cell lines that synthesize antibody directed against a human tumor-associated fetal antigen designated as oncofetal antigen-I (OFA-I), a method is described for the production of IgM anti-OFA-I in vitro. Ten serum samples containing high levels of anti-OFA-I were identified and viably frozen peripheral-blood lymphocytes (PBL) from the same patients were transformed by Epstein-Barr virus (EBV). Patients included five given adjuvant immunotherapy with an OFA-I+ tumor-cell vaccine (TCV), three treated with BCG, and two treated only by surgical excision. Anti-OFA-I levels in the spent medium were monitored by immune-adherence using the OFA-I+ melanoma cell line UCLA-SO-M14 (M14), as the target cell. Two of the EBV-infected cultures (ES from the TCV group and CD from the surgery only group) produced detectable antibody to M14 cells by day 6. By day 9, culture DV (BCG group) became positive. The CD culture was positive only for 9 days, while ES (obtained from the patient with the highest anti-OFA-I titer) ceased growth after 3 wk. The supernatants displayed no reactivity against a control lymphoblastoid cell line autologous to the M14 donor. The DV lymphoblasts continued to produce increasing titers of anti-M-14 antibody until day 42, with gradual decrease by day 60 and became negative on day 66. None of the other 7 PBL cultures became positive to M14. Further studies determined that the antibody exhibited specific reactivity to an antigen associated with human cancer. No antibody reactivity in the DV culture medium was detected to a number of target cells tested. Assessment of the immunoglobulin class indicated the anti-OFA-I was limited to the IgM class. The DV spent medium was cytotoxic in the presence of either rabbit or human complement. (21 Refs)

104. PURIFICATION OF CYTOPLASTS (ENUCLEATED CELLS) AND KARYOPLASTS (NUCLEI) FROM MOUSE SPLENIC LYMPHOCYTES WITH CYTOCHALASIN-B.

Ohara J, Sekuguchi T, Watanabe T
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J Immunol Methods; 45(3):239-248 1981

Murine spleen and lymphoma cells were almost completely enucleated in suspension by centrifugation in discontinuous Ficoll gradients in the presence of cytochalasin-B. Viability of cytoplasts (cells lacking nuclei) and karyoplasts (nuclei) was over 90%. Pure fractions of cytoplasts or karyoplasts were then obtained by fractionation of the cytochalasin-B treated cells with unit gravity sedimentation in bovine serum albumin. Protein synthesis was seen in cytoplasts when they were stimulated with mitogens, such as lipopolysaccharide (LPS). This method can consistently yield pure fractions of morphologically and functionally intact karyoplasts or cytoplasts from normal lymphocytes with very low contamination of nucleated cells. Pure karyoplasts or cytoplasts obtained in this way should be extremely useful for subcellular analysis of lymphocyte activation. (Author abstract) (11 Refs)

105. SCREENING SYSTEM FOR THE EVALUATION OF PREPARATIONS WITH POTENTIAL CYTOSTATIC AND IMMUNOTROPIC ACTIVITY. III. DERIVATIVES OF HEXAHYDROCHROMATE.

Gieldanowski J, Steuden W
Dept. Experimental Therapy, Inst. Immunology and Experimental Therapy, Polish Acad. Sciences, Czerska 12, 53-114 Wroclaw, Poland
Arch Immunol Ther Exp (Warsz); 29(2):267-271 1981

Eleven hexahydrochromate derivatives were evaluated for their effects on phytohemagglutinin-induced lymphocyte transformation. Most derivatives (eg, cyanide compounds) showed weak activity in inhibiting 14C-thymidine incorporation in cell nuclei. Some compounds suppressed the blastic reaction at high concentrations and stimulated it at low concentrations; in some cases, the suppression resulted from a preparation's effect on medium pH. The experimental system can detect a compound's affinity for nucleic acids and should be useful in screening new compounds for their antimitotic and immunosuppresive activity. (9 Refs)

106. EVALUATION OF MICROAUTORADIOGRAPHIC AND LIQUID SCINTILLATION METHODS IN THE STUDY OF LYMPHOCYTE TRANSFORMATION..

Zhang L, Wang E, Tian D, Liu J
Dept. Microbiology, Suzhou Medical Coll., Suzhou, People's Republic of China
Zhonghua Zhongliu Zazhi; 3(1):45 1981

Lymphocyte transformation tests are not only important in immunologic research, their application in clinical medicine has received increasing recognition. A comparative study of three methods are described: microautoradiography, liquid scintillation counting and direct smears (morphological examination). Cultured T-lymphocytes from the peripheral blood of 20 normal subjects (ages 40-60 yr) were used along with H3-TdR. Results showed microautoradiography to be the best method. (no Refs) (In CHI)

107. A SIMPLE METHOD FOR THE QUANTITATION OF SPECIFIC CYTOTOXIC PRECURSORS TO SYNGENEIC TUMORS.

Teh HS, Kwong L, Yu M, Kilburn DG
Dept. Microbiology, Univ. British Columbia, Vancouver, British Columbia V6T 1W5, Canada
J Immunol Methods; 46(1):97-111 1981

Cytotoxic T lymphocytes (CTLs) to EL4, a syngeneic lymphocytic leukemia of C57BL/6 (H-2b) mice, were obtained by culturing normal B6 spleen cells with irradiated EL4 tumor cells for 4 days in conical bottom microtiter trays. A much lower, though significant, amount of cytotoxicity towards EL4 was observed in B6 spleen cell cultures not stimulated with EL4. The cytotoxic effector cells were shown to be Thy-1+ and their cytolytic activity to EL4 tumor cells was inhibited by an anti-H-2b serum. Cold target competition studies suggest that the B6 anti-EL4 CTLs could discriminate between EL4 tumor cells and a second H-2b lymphoma, C1498. the converse experiment yielded similar results. Culture conditions limiting for CTL precursors (CLPs) to EL4 were attained by including interleukin 2 (IL2), a lymphokine obtained by stimulating murine or rat spleen cells with concanavalin A, in the culture medium. In the presence of IL2, the CLP frequencies in B6 spleen cells to EL4 and C1498 in antigen-stimulated cultures were 113 and 231 per 10(6) responder cells, respectively. In non-antigen-stimulated B6 spleen cell cultures, the apparent CLP frequencies to EL4 and C1498 were 6 and 33 per 10(6) responder cells, respectively. In agreement with the cold target competition studies using CTLs generated in the absence of IL2, we found that the CTL clones produced in cultures stimulated with EL4 and C1498 in the presence of IL2 were specific for the stimulating antigen. The specificity of the CTL clones obtained from cultures stimulated with IL2 in the absence of antigen appears to be different from those derived from antigen-stimulated cultures. The potential applications and limitations of this culture system are discussed. (Author abstract) (32 Refs)

108. EFFECTS OF METALS IN IN VITRO BIOASSAYS.

Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

In vitro bioassays for detecting the mutagenicity and potential carcinogenicity of metal compounds are reviewed. Assays discussed include the Salmonella typhimurium and Escherichia coli assays that quantitate the ability of metals to revert the bacteria to histidine prototrophy and to tryptophan prototrophy, respectively, and the use of Bacillus subtilis strains deficient in DNA repair to determine growth inhibitory effects of metals. Other bioassays examine the ability of metals to induce thioguanine or azaguanine resistance in Chinese hamster cells, enhance viral transformation in hamster cells, transform Syrian hamster cells, and induce chromosome aberrations in hamster and rat cells and human lymphocytes. Correlations between in vitro bioassays and in vivo carcinogenicity are discussed. (82 Refs)

SUPPRESSOR CELL ACTIVITY

109. THE MODE OF ACTION OF SPLENIC SUPPRESSOR CELLS IN MURINE PLASMACYTOMA.

Chen Y, Heller P
Veterans Admin. West Side Medical Center, PO Box 8195, Chicago, IL, 60680
Clin Exp Immunol; 45(3):514-522 1981

Polyclonal IgM secretion after LPS stimulation and antigen-dependent antibody production by splenic cells of BALB/c mice with plasmacytoma were found to be markedly reduced. The former occu rred without mediation of suppressor cells, probably as the result of a quantitative reduction of mitogen-responsive B lymphocytes. On the other hand, the reduction in the generation of antibodies to sheep RBC in vitro, as determined by the number of PFC, was found to be dependent on the activity of suppressor cells which had the functional characteristics of macrophages. The targets of these suppressor cells were found to be normal macrophages, B and T lymphocytes which were all independently suppressed. A diffusible factor appeared to be responsible for the suppressive effect of the suppressor macrophages interfering mainly with those early stages of the immune response involving antigen-triggered B cell activation. (Author abstract) (30 Refs)

OTHER RELATED STUDIES

110. HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE ACTIVITY IN NORMAL AND LEUKAEMIC LYMPHOCYTES.

Rambotti P, Davis S
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Br J Haematol; 49(1):23-28 1981

The levels of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) were determined in lymphocytes from normal people and patients with chronic lymphocytic leukemia (CLL). The HGPRT level in the total lymphocyte population from patients with CLL was lower than that from normal subjects. The HGPRT activity was higher in normal non-T cells than normal T cells. The enzyme activity in CLL B cells was lower than in CLL T cells. The HGPRT level was higher in CLL T cells than in normal T cells; these data suggest CLL T cells differ biochemically from their normal counterparts. (Author abstract) (17 Refs)

111. EXAMINATION OF HEMATOPOIETIC STEM CELLS IN LEUKEMIA IN CHILDREN (MEETING ABSTRACT).

Saito K, Ando H, Yagi Y, Norose N, Koike K, Nakahata R, Akahane T
Dept. Pediatrics, Faculty Medicine, Shinshu Univ., Matsumoto-shi, Nagano Prefecture 390 Japan
Program and Abstracts of the 84th Annual Congress of Japan Pediatric Society held in Tokushima, Japan, 15-17 May, 1981. Japan Pediatric Society, Tokyo 160, Japan, 398 pp., 1981.

The bone marrow and peripheral blood of 61 children with acute lymphatic leukemia, 18 with acute blastocytic leukemia, 26 with acute myelogenous leukemia, 3 with acute monocytic leukemia, 2 with adult chronic myeloid leukemia and 1 with juvenile chronic myeloid leukemia were examined for changes in the hematopoietic stem cells during the course of the disease. The bone marrow and blood obtained from five patients with nonhemopathy were used as the control. The colony forming units in culture (CFU-C) and CFU in RBC (CFU-E) were markedly decreased during progressive period of acute leukemia. CFU mixture cells were seen in one patient. The av value of CFU-C and CFU-E was slightly reduced at the partial remission period. There was no significant difference between the hematopoiesis of the patients with leukemia at the period of complete remission, and that of the control. CFU-C was decreased in the patient who had relapse within 2 mo after examination. Colony formation (CFU-C and CFU-E) was within the normal range for the patients who were off therapy. The effect of leukemia cells on CFU-C was examined by mixing 1-2 x 10(5) ml of the cells with the control myeloid cells before the reaction. No significant difference was seen in the number of colonies formed with or without the addition of the blastocytes. Therapy to introduce remission consisting of L-asparaginase decreased the number of colonies, but not significantly. There was no clear difference between any of the maintenance therapy protocols in their effect on hematopoiesis. Irradiation of the skull and mediastinum did not inhibit colony formation. The CFU-C in the peripheral blood was increased in adult chronic myelogenous leukemia. In juvenile chronic myelogenous leukemia the CFU-C of the bone marrow and peripheral blood was increased. Most of the colonies consisted of monocytes and macrophages. (no Refs) (In JPN)

112. DIFFERENTIATION OF MOUSE MYELOID LEUKEMIA CELLS INDUCED BY 1ALPHA,25-DIHYDROXYVITAMIN D3.

Abe E, Miyaura C, Sakagami H, Takeda M, Konno K, Yamazaki T, Yoshiki S, Suda T
(c/o Suda) Dept. Biochemistry, Sch. Dentistry, Showa Univ., 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan
Proc Natl Acad Sci USA; 78(8):4990-4994 1981

Mouse myeloid leukemia cells can be induced to differentiate into macrophages in vitro by 1alpha,25-dihydroxyvitamin D3, the active form of vitamin D3. The minimal concentration of 1alpha,25-dihydroxyvitamin D3 to induce the cell differentiation was 0.12 nM. The degree of cell differentiation in various markers induced by 12 nM 1alpha,25-dihydroxyvitamin D3 was nearly equivalent to that induced by 1 uM dexamethasone, the most potent known stimulator. Among several markers of the differentiation by 1alpha,25-dihydroxyvitamin D3, phagocytic activity was induced within 24 hr, and this was followed by induction of lysozyme and locomotive activities. Similar changes were also induced by 0.01-1.00 uM 1alpha-hydroxyvitamin D3. 25-Hydroxyvitamin D3 and 24R,25-dihydroxyvitamin D3 showed only weak inducing activity. These results suggest the possibility that, in addition to its well-known biological activities in enhancing intestinal calcium transport and bone mineral mobilization, 1alpha,25-dihydroxyvitamin D3 is involved in the differentiation of bone marrow cells. (Author abstract) (27 Refs)

113. NORMAL AND LEUKEMIC GRANULOPOIESIS.

Gavosto F, Aglietta M
I Cattedra di Patologia Medica, Universita degli Studi di Torino, Corso Polonia, 14, 10126 Torino, Italy
Haematologica (Pavia); 66(1):1-17 1981

This editorial reviews current understanding of the development of normal and leukemic cells. The supply of normal blood cells must be continuously replenished. This is accomplished by the totipotential stem cell, described as a colony-forming-unit-spleen because it forms splenic colonies in irradiated animals. Strong cytogenetic and enzymatic evidence suggests that myeloid leukemias represent monoclonal expansion of a single transformed cell; in chronic form, the transforming event probably affects a pluripotent stem cell. Whether this occurs in acute myelocytic leukemia, or instead primary transformation occurs in the granulocyte-oriented cell is not certain. Granulopoiesis represents the most altered differentiative line; growth models and response to regulation factors of granulocyte-monocyte-oriented stem cells have been studied to learn about prognosis and pathogenesis of uncontrolled leukemic proliferation. Recent experiments by the authors suggest that prostaglandins might be important in granulo-monocytopoiesis. Insensitivity to prostaglandins may be one of the main causes of uncontrolled leukemic proliferation. (71 Refs) (In ITA)

114. AUTOSTIMULATION OF GROWTH BY HUMAN MYELOGENOUS LEUKEMIA CELLS (HL-60).

Brennan JK, Abboud CN, DiPersio JF, Barlow GH, Lichtman MA
Hamatology Unit, Dept. Medicine, Univ. Rochester Medical Center, 601 Elmwood Ave., Rochester, NY, 14642
Blood; 58(4):803-812 1981

We have studied the effects of medium conditioned by the human progranulocytic leukemia cell line, HL-60, on the subsequent growth of new inocula of HL-60 cells. When HL-60 cells were cultured at high cell density, optimal growth rate occurred in liquid suspension and confluent colony growth was observed in viscous medium without the addition of conditioned medium. However, when cells were cultured at lower cell density, growth rate was reduced and colony growth was nil unless conditioned medium from HL-60 culture was added. All HL-60 populations studied, including the earliest available passage, 9, both elaborated and responded to HL-60 CM. HL-60 CM did not stimulate normal human or mouse granulocyte-monocyte colony-forming cell (CFU-GM) growth. Conditioned media from other human cell lines varied in the ability to stimulate HL-60 cell and CFU-GM proliferation. Some, such as GCT CM, stimulated both HL-60 cells and normal CFU-GM, whereas others, like HL-60 CM, stimulated only HL-60 growth. The majority of cell line CMs tested did not stimulate either HL-60 or CFU-GM. Chromatography of HL-60 CM on Ultrogel AcA54 showed a single peak of HL-60 stimulating activity of apparent mol wt 13,000. The ability of HL-60 cells to elaborate this activity provides a possible explanation for their proliferation at higher cell densities. Autostimulation may prove to be important in the high growth potential of other cell populations that undergo unrepressed proliferation. (Author abstract) (49 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abboud CN 114
Abe E 112
Abe S 89
Adler WH 25
Aglietta M 113
Akabane T 111
Ando H 111
Andrus L 86
Anvret M 54
Aozasa K 9
Arai T 75
Arlin Z 21
Athanassiades T 73
Aur RJ 23
Avila C 37
Aziz GJ 71
Baba K 89
Bandai H 9
Bandekar JR 85
Bandyopadhyay C 85
Barlow GH 114
Bartnik W 16
Bazin H 63
Becker H 100
Berg K 99
Berney JJ 94
Beverley P 100
Bigner DD 71
Bistrian BR 31
Bjorkholm M 45
Blackburn GL 31
Bloom BR 81
Bowman WP 23
Brennan JK 114
Brooks WH 71
Brosman S 20
Bruley-Rosset M 90
Brusse E 65
Bugelski PJ 97
Businco L 57
Butler M 17
Carchman RA 83
Catovsky D 51
Cazenave PA 82
Chander R 85
Chen Y 109
Chen YC 26
Chessels J 57
Chlopkiewicz B 1
Chu FC 34
Chui C 34
Churbakova EV 95
Clarkson BD 21
Collins R 54
Cox JD 41
Crawford DH 36
Crowther D 19
Custardoy Motil 37
Davies MD 62
Davis S 110
De Landazuri MO 7
Delia D 40
Deng JS 26
Devesa Mugica J 37
DiPersio JF 114
Diehl V 33
Dmoszynska-Gian 2
Dorey F 20
Doskocz W 14
Dougherty TJ 97
Dye ES 72
Edwards AJ 36
Enriquez Valens 37
Ernberg I 45
Ernberg I 47
Ernberg I 57
Faanes RB 79
Fahey JL 20
Ferrer JF 74
Fidler IJ 93
Finegan D 34
Fishman M 92
Florentin I 90
Foa R 51
Francis GE 36
Francis GE 94
Froussard P 18
Fukushi F 91
Gale RP 48
Galton DA 51
Gartner JG 46
Gavosto F 113
Gerdes J 33
Gibson C 19
Gidlund M 53
Gieldanowski J 105
Gieldanowski J 14
Gieldanowski J 15
Gillis S 61
Glomstein A 57
Gobbi PG 6
Goldstein G 36
Goldstein G 40
Gorczyca W 14
Gottleib AA 8
Granato D 29
Greaves M 40
Greaves MW 68
Grimm EA 22
Grossbard E 34
Gupta P 74
Hamilton TA 92
Hancock EJ 78
Hanto D 54
Hariri G 40
Harvey KB 31
Hegedus C 96
Heller P 109
Henle G 45
Henle G 55
Henle G 57
Henle W 45
Henle W 55
Henle W 57
Henney CS 61
Henriksen D 84
Henry K 24
Herberman RB 7
Hercend T 90
Herr HW 35
Hirashima M 81
Hirose M 49
Hjtzig WH 52
Hoffbrand AV 36
Hoffbrand AV 94
Hokland P 99
Holland JF 21
Holowiecki J 12
Hopfan S 34
Hu G 30
Iguchi S 69
Inoshita T 5
Irie RF 103
Irmscher H 60
Ise T 49
Ishizaka K 81
Ito H 9
Izotova TA 3
Jacobsen F 102
Janossy G 36
Janssens M 63
Japa J 12
Jarczok K 12
Jeljaszewicz J 77
Johansson B 45
Joller PW 52
Joncas JH 46
Jones PC 103
Juy D 82
Kapoor L 34
Kasage S 75
Katz SI 80
Kemshead J 40
Kenyon SJ 74
Kern DE 61
Kessler FK 83
Kessler L 60
Kiger N 66
Kikuchi K 69
Kilburn DG 107
Kilburn DG 78
Kim JH 34
Kirchner H 33
Klein E 47
Klein G 44
Klein G 45
Klein G 54
Klein G 56
Klein G 57
Knopf B 32
Knothe J 60
Ko HL 77
Koike K 111
Kojima T 39
Konno K 112
Kopper L 96
Koziner B 21

Koziorowska J 1
Krawczyck M 12
Kronstrom H 66
Kruger W 70
Kufe DW 50
Kung P 40
Kung PC 36
Kurtenkov OA 58
Kwong L 107
Lafferty KJ 86
Lanzer G 100
Lapis K 96
Laskin DL 83
Laskin JD 83
Lattanzio G 6
Lauria F 51
Layward L 17
Le Guern C 82
Lee T 98
Lenskaia RV 3
Leventhal BG 43
Levinsky RJ 17
Levy JG 78
Levy SB 18
Lichtman MA 114
Lie S 57
Lin Y 30
Liu C 30
Liu J 106
Longo DL 27
Lopez-Botet M 7
Lotze MT 22
Luger TA 80
Maj S 1
Major P 50
Markesbery WR 71
Maryamma KI 67
Masucci G 45
Masucci G 47
Masucci G 57
Masucci MG 45
Masucci MG 47
Masucci MG 57
Mathe G 90
Matsumoto S 76
Mauer AM 23
Mazumder A 22
McConnell I 36
McIntyre RE 48
Mellstedt H 45
Melvin SL 23
Mendelsohn N 21
Mentkevich LM 95
Merlini G 6
Miliukhina LM 58
Minoda K 39
Mitelman F 28
Mitelman F 42
Miyaura C 112
Mizuno D 89
Mohan R 34
Moldawer LL 31
Morales Castine 37
Morstyn G 101
Morton DL 103
Moschella S 50
Musso LA 10
Nachbar MS 84
Nagai M 75
Nakade J 98
Nakahata R 111
Nakamori H 98
Nerkar DP 85
Nilsson K 53
Noltenius HW 59
Norose N 111
North RJ 72
O'Reilly RJ 34
Ohara J 104
Ohira M 49
Okada M 61
Okuda M 4
Olson C 64
Olsson L 66
Omiya A 49
Oppenheim JD 84
Oppenheim JJ 80
Orn A 53
Ortaldo JR 7
Pagano JS 46
Pang RH 84
Parker D 68
Parrott DM 62
Pattengale PK 53
Pearson G 45
Pearson G 57
Perugini S 6
Perussia B 29
Pituch-Noworols 13
Platteau B 63
Pluss HJ 52
Porter CW 97
Prentice HG 36
Primi D 82
Pulverer G 77
Purtilo D 44
Purtilo DT 54
Purtilo DT 56
Purtilo DT 57
Rajan A 67
RamachandranKM 67
Rambotti P 110
Rao J 40
ReMine SG 16
Reece ER 46
Reid A 34
Reitnauer PG 70
Rose H 65
Rosenberg SA 22
Roszkowski K 77
Roszkowski W 77
Roszman TL 71
Rubinstein DB 27
Rudzka E 12
Rumiantsev AG 3
Rupniewska ZM 2
Saemundsen AK 54
Saito K 111
Sakagami H 112
Sakaguchi K 4
Sakamoto K 54
Sakamoto K 57
Sako H 98
Samochatova EV 3
Sanchez P 82
Santoli D 29
Sasaki J 91
Sato O 69
Saxena RK 25
Saxon A 48
Schaadt M 33
Secher D 36
Sedlmayr P 100
Seemayer TA 46
Sekuguchi T 104
Shank B 34
Shorter RG 16
Sidell N 103
Sieff C 57
Simmons R 54
Sirover MA 108
Skowronska J 14
Spees EK 25
Spina CA 20
Sreekumaran T 67
Stadler BM 80
Stein H 33
Stella-Holowiec 12
Steuden W 105
Steuden W 14
Steuden W 15
Stevens RH 48
Strausser JL 22
Suda T 112
Sugawa T 98
Sulllivan JL 54
Sulochana S 67
Sundstrom C 53
Susskind BM 79
Sutherland R 40
Svedmyr E 45
Svedmyr E 47
Svet-Moldavskay 21
Svet-Moldavsky 21
Synnerholm AC 54
Szigeti R 45
Szigeti R 47
Szigeti R 57
Takashima I 64
Takeda M 112
Targan SR 87
Tautt J 1
Teh HS 107
Tempelis LD 18
Tewari GM 85
Thatcher N 19
Thorn RM 74
Tian D 106
Tilz GP 100
Timar J 96
Timonen T 7
Tomiyama S 4
Tosca N 68
Tran-van-Hanh 96
Trinchieri G 29
Tuma GA 94
Turk JL 68
Uede T 69
Umesaki N 98
Vadas MA 101
Valsala KV 67
Vella Briffa D 68
Verbi W 40

Vescera C 20
Vikram Reddi M 67
Vilcek J 84
Von Ardenne M 70
Wagstaff J 19
Wang E 106
Watanabe T 104
Watzig V 32
Wauters G 63
Weinstein IB 83
Whiteside TL 5
Whittingham S 101
Wick MM 50
Wigzell H 53
Wilson JW 101
Wing MA 36
Wu YT 47
Yagi Y 111
Yamada Y 88
Yamamoto S 9
Yamazaki T 112
Yasuda S 75
Yip YK 84
Yodoi J 81
Yoshiki S 112
Yoshino J 38
Young LS 11
Yu M 107
Zafar MN 51
Zeng Y 30
Zerebeckyj-Eckh 84
Zhang L 106
Zhao W 30
Zinzar SN 21

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In this issue:

- **EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS** 1-49
- **EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS** 50-61
- **EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION** 62-87
- **THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE** 88-93
- **ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY** 94-96
- **RELATED BIOLOGY OF IMMUNE CELLS** 97-107
- **CMI METHODOLOGY** 108-110
- **SUPPRESSOR CELL ACTIVITY** 111

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20. 3173/2:

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. PLASMA CONCENTRATIONS OF PREGNANCY-ASSOCIATED ALPHA-2-GLYCOPROTEIN IN PATIENTS WITH LEUKAEMIA.

Thomson AW, Lessels SE, Horne CH
Dept. Pathology, Univ. Medical Bldg., Foresterhill, Aberdeen AB9 2ZD, Scotland
Acta Haematol (Basel); 66(3):210-213 1981

Plasma concentrations of pregnancy-associated alpha2-glycoprotein (alpha2-PAG) were estimated by electroimmunoassay in 64 patients with various leukemias. Seven percent (2/30) of male patients and 28% (9/32) of female patients had alpha2-PAG levels above the established upper limit for age- and sex-matched controls. There was no indication that these elevated alpha2-PAG concentrations were related to type of leukemia and no correlation between the circulating levels of alpha2-PAG and the absolute lymphocyte or monocyte counts was found. (Author abstract) (19 Refs)

2. IMMUNOLOGICAL ALTERATIONS IN PATIENTS WITH HODGKIN'S DISEASE IN CLINICAL REMISSION AND RELAPSE.

Ruibal Ares B, Sasiain Mdel C, Brezavscek DM, Fejes M, Bachman AE
Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Las Heras 3092, 1425 Buenos Aires, Argentina
Medicina (B Aires); 41(3):287-292 1981

Of 35 Hodgkin's disease patients, 21 were in remission (12-77 yr old, av 44.2 yr; 15 men and 6 women) and 14 had clinical symptoms. The relapse patients (19-76 yr old, av 40.3 yr) were: six with firm nodules, six with mixed cellularity, and one with lymphocyte depletion. Remission patients were: 16 with mixed cellularity, 3 firm nodules, and 2 with lymphocyte prevalence. Following tests were performed: proteinogram, microimmunoelectrophoresis (MIE), EAC and E rosettes, anti-Epstein Barr virus (EBV) antibody titers (anti-viral capsid antigen and anti-Epstein Barr nuclear antigen), phytohemagglutinin (PHA) stimulation, purified protein derivative (PPD) skin test, and mixed lymphocyte culture (MLC) against HRIK lymphoblastoid cell line. All patients showed significant decrease in the absolute number of T lymphocytes and EAC rosettes, but high anti-EBV antibodies (especially during clinical relapse). Patients in relapse had low PHA response, low MLC value, and negative skin test. Alterations in MIE were evident in 13 patients. Hodgkin's disease relapse patients showed severe immunity alterations. (17 Refs) (In SPA)

3. USE OF IMMUNOLOGICAL METHODS IN CHARACTERIZING ACUTE LYMPHOBLASTIC LEUKEMIAS IN CHILDHOOD.

Cap J, Babusikova O, Misikova Z, Foltinova A
II. Detska klinika, Detska fakultna nemocnica, Duklianska 14, 881 25 Bratislava, Czechoslovakia
Bratisl Lek Listy; 76(2):183-191 1981

Spontaneous and immune rosette tests were performed in 47 children (3-14 yr old) with acute lymphoblastic leukemia (ALL). The tests were performed at the time of diagnosis in 26 cases, and during complete remission in the course of cytostatic therapy in 21. Immunological classification of ALL was possible in 16 cases: null cell type was found in 10 cases, B cell type in 2, T cell type in 1, and T + B cell type in 3. During the 4-30-mo follow-up period there were no differences in the course of the disease between the individual immunological types. Repeated rosette tests showed normalization of the T and B lymphocyte counts shortly after remission had been achieved. In the further course, the T cell count tended to decrease, reaching normal levels only after completion of the cytostatic therapy, while the B cell count remained within the normal range. (20 Refs) (In SLO)

4. PHENOTYPIC EVALUATION OF CHRONIC MYELOID LEUKEMIA.

Moore MA, Mertelsmann R, Pelus LM, Van Bekkum DW, McCulloch EA, Gallo R, Lajtha L, Ross D, Breton-Gorius J, Greaves MJ, Boggs D, Fauser AA, Stryckmans P

Dept. Developmental Hematopoiesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Blood Cells; 7(2):217-236 1981

Marrow cultures from patients in the chronic phase and blastic crisis of chronic myeloid leukemia (CML) revealed a spectrum of qualitative and quantitative defects in granulocyte-macrophage progenitors (GM-CFC). Parallel culture studies and determination of terminal deoxynucleotidyl transferase (TdT) values revealed that many patients in blastic CML crisis possessed two coexisting acute phase clones, one lymphoblastic, the other myeloblastic. Leukemic blast cells from patients with TdT-positive blastic crisis produced T cell growth factor, but did not exhibit proliferative response to exogenous factor. This phenotype was identical to that in TdT-positive acute lymphoblastic leukemia. Leukemic GM-CFC proliferation in CML was resistant to concentrations of prostaglandin E which caused marked inhibition in normal bone marrow cells. The self-renewal or recloning capacity of GM-GFC was also identified as a unique feature of some CML patients. Addition of retinoic acid to primary cultures of leukemic GM-GFC completely abolished this recloning capacity. (33 Refs)

5. IMMUNOLOGICAL PHENOTYPES OF HUMAN LEUKEMIAS OF THE B-CELL LINEAGE.

Seligmann M, Vogler LB, Prud'homme JL, Guglielmi P, Brouet JC, Gallo R, Cronkite EP, Lajtha L, Dreyfus B, Ross D, Debre P, Greaves MJ

Lab. Immunochemistry and Immunopathology, Hopital Saint Louis, 75475 Paris 10, France

Blood Cells; 7(2):237-246 1981

Some recent immunological studies of various B-cell lineage human leukemias performed in the authors' laboratory are reviewed. Study of pre-B leukemias has shown the diversity of immunoglobulin expression in leukemic cells resembling B-lymphocyte precursors and has provided insights into the biology of progenitor cells. Acute leukemia with Burkitt cells is a homogenous group close to classical Burkitt's lymphoma. Leukemic cells from chronic lymphocytic-B leukemia and hairy cell leukemia can be induced to differentiate under the influence of mitogens. Hairy cells were able to express new phenotypic characteristic after phytohemagglutinin stimulation. (28 Refs)

6. GROWTH OF HUMAN NORMAL AND LEUKEMIC T CELLS: T-CELL GROWTH FACTOR (TCGF) AND THE ISOLATION OF A NEW CLASS OF RNA TUMOR VIRUSES (HTLV).

Gallo RC, De The, Lajtha L, Van Bekkum DW, McCulloch EA, Greaves MJ, Seligmann M , Brecher G, Shohet SB, Bessis M, Sachs L
Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Blood Cells; 7(2):313-329 1981

Previous studies have indicated that T-cell growth factor (TCGF) is the physiological growth promoter in the immune response of T-lymphocytes, acting as the second signal (after antigen) in the immune response. A summary is presented of information on proliferation of normal T-cells in a previously described liquid suspension culture and proliferation of several new cell lines from patients with particular types of T-cell leukemias and lymphomas. Information on the new type-C virus designated HTLV is also summarized. Neoplastic T cells from patients with cutaneous T-cell leukemias and and lymphomas, eg Sezary syndrome and mycosis fungoides, were grown routinely with the use of purified TCGF free of phytohemagglutinin and of lymphokines other than TCGF. The neoplastic T cells responded directly to TCGF without prior in vitro activation with antigen or lectin as is necessary with normal T cells. Thus, transformed mature T cells already express TCGF receptors. HTLV were isolated from some of these new cell lines. Evidence is presented to indicate these may be the first unambiguous isolates of RNA tumor viruses from humans. These new viruses are easily distinguished from all previously isolated viruses from animals. Antibodies in sera of some patients with these diseases specifically react with proteins of these viruses. (11 Refs)

7. B LYMPHOCYTE FUNCTION IN B CELL CHRONIC LYMPHOCYTIC LEUKAEMIA.

Wolos JA, Davey FR
(c/o Davey) Div. Clinical Pathology, State Univ. New York Upstate Medical Center, 750 East Adams Street, Syracuse, NY, 13210
Br J Haematol; 49(3):395-403 1981

B-enriched lymphocyte populations from patients with chronic lymphocytic leukemia (CLL) were compared to B-enriched lymphocyte populations from normal age-matched controls for their ability to stimulate a proliferative response and to generate cytotoxic cells in allogeneic mixed lymphocyte cultures (MLC). The proliferative responses of MLCs were less than normal when the stimulating cells originated from B cells of patients with CLL. The degree of stimulation provided by the B cells from the patients with CLL inversely correlated with the peripheral white cell count. Lymphocytes from patients providing a poor stimulatory signal in the MLC tended to have less 'Ia-like' antigen than lymphocytes giving a moderate level of stimulation. B lymphocytes from patients with CLL which stimulated poorly in the MLC also failed to generate specific cytotoxic cells even when provided with a normal proliferative trigger. These data suggest that B lymphocytes from cases of CLL with markedly elevated WBC counts may have a diminished concentration of both 'Ia-like' and serum defined antigens. (Author abstract) (27 Refs)

8. A VIRUS ASSOCIATED WITH HUMAN ADULT T-CELL LEUKAEMIA.

Weiss R
Inst. Cancer Res., London, England
Nature; 294(5838):212 1981

Recent virological, serological and epidemiological evidence strongly indicates that a newly discovered retrovirus is the etiological agent of certain types of adult T-cell lymphoma/leukemia. The virological evidence first came from RC Gallo's laboratory at the US NCI where the retrovirus was isolated from a T-lymphoma cell line established in culture from a patient with mycosis fungoides. In this issue of Nature Poiesz et al report the isolation of a similar virus from a patient with Sezary syndrome, while Kalyanaraman et al show that the two patients' sera (and that of a patient's spouse) contain antibodies which specifically react with the major core protein of the virus. Mycosis fungoides and Sezary syndrome are clinical variants of cutaneous T-cell lymphoma and leukemia, respectively, that occur as rare diseases in adults. The retrovirus particles produced by these tumors are not evident until the tumor cells are grown in culture, although a second biopsy from the first patient released virus within 24 hr of its being placed in culture. Until 5 yr ago it was very difficult to maintain normal or malignant T cells in culture; however, a specific T-cell growth factor (TCGF) discovered in Gallo's laboratory enables T cells to proliferate in vitro for long periods, and this aided the detection of the virus. (Author abstract) (12 Refs)

9. ISOLATION OF A NEW TYPE C RETROVIRUS (HTLV) IN PRIMARY UNCULTURED CELLS OF A PATIENT WITH SEZARY T-CELL LEUKAEMIA.

Poiesz BJ, Ruscetti FW, Reitz MS, Kalyanaraman VS, Gallo RC
Lab. Tumor Biology, NCI, NIH, Bethesda, MD, 20205
Nature; 294(5838):268-271 1981

A new type C retrovirus (HTLV-mb) has been isolated from a cell line from a 64-yr-old black female patient, MB, with the leukemic phase of Sezary syndrome. This cell line, CTCL-2 was established with use of partially purified T-cell growth factor from a sample of her peripheral blood. These cells have produced typical type C particles from the earliest passage studied (passage 2) but only after induction with 5-iodo-2'-deoxyuridine. The fractions containing HTLV-mb particles were identified by electron microscopy and by assaying for reverse transcriptase. Proteins and nucleic acid of HTLV were also identified in the fresh, uncultured, Sezary leukemic blood cells from which the second isolate was obtained. Analysis of the proteins and nucleic acids of this retrovirus isolate indicate close relationship to HTLV-cr, a retrovirus recently isolated and characterized from a patient with cutaneous T-cell lymphoma (mycosis fungoides) but distinct from known animal retroviruses. (23 Refs)

10. G1-PHASE ARREST OF CULTURED HUMAN LEUKEMIC T-CELLS INDUCED BY DEOXYADENOSINE.

Fox RM, Kefford RF, Tripp EH, Taylor IW
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Cancer Res; 41(12):5141-5150 1981

Cultured human T-cell leukemia lymphocytes have enhanced sensitivity to growth inhibition by deoxyadenosine. We have used flow cytometry to investigate the mechanism of deoxyadenosine toxicity in cultured T-leukemic cells. Comparative studies on deoxyadenosine-resistant Epstein-Barr virus-transformed B-lymphocyte cell lines were also performed. After exposure of T-cells to low concentrations of deoxyadenosine (3 uM), in the presence of an adenosine deaminase inhibitor (erythro-9-[3-(2-hydroxynonyl)]adenosine), accumulation of cells of cells with a G1 DNA content was demonstrated. In contrast, B-cell lines showed a similar degree of growth inhibition after exposure to 200 to 400 mM deoxyadenosine but were blocked in S phase. The T cell G1 block was associated with a rise in the deoxyadenosine triphosphate pool, and both these phenomena were prevented by the addition of deoxycytidine. The biochemical mechanisms of this G1 block induced by deoxyadenosine in T-cells is not understood. (Author abstract) (25 Refs)

11. DIFFERENT RESPONSIVENESS OF COLONY-FORMING CELLS FROM NORMAL SUBJECTS AND CHRONIC MYELOID LEUKEMIA PATIENTS TO 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

Pegoraro L, Bagnara G, Bonsi L, Biagini G, Garbarino G, Pagliardi GL
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Cancer Res; 41(12):5049-5051 1981

The effects of 12-O-tetradecanoylphorbol-13-acetate (TPA), a potent inducer of differentiation, upon the in vitro proliferation of normal bone marrow and chronic myeloid leukemia granulocyte-macrophage progenitor cells were investigated in the presence or absence of exogenous colony-stimulating activity. In the absence of colony-stimulating activity, no colony formation occurred, whereas its presence was followed by the appearance of colonies almost exclusively composed of macrophagic cells. However, both normal and leukemic granulocyte-macrophage progenitor cells showed a different response to TPA in terms of colony number and size. The number of colonies obtained from normal bone marrow was reduced to about 45% at three TPA concentrations (1 x 10(-8), 1 x 10(-10), and 1 x 10(-12) M). By contrast, the plating efficiency of leukemic granulocyte-macrophage progenitor cells was not significantly affected by 1 x 10(-10) and 1 x 10(-12) M TPA, but was strongly reduced by 1 x 10(-8) M. Moreover, TPA treatment did not significantly influence the size of colonies from normal bone marrow, while at 1 x 10(-10) and 1 x 10(-12) M, it remarkably increased that of the leukemic colonies. These different responses to TPA can be related to the abnormal sensitivity of chronic myeloid leukemia stem cells to factors regulating proliferation. (Author abstract) (24 Refs)

12. T-LYMPHOCYTE SUBPOPULATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA: A QUANTITATIVE AND FUNCTIONAL STUDY.

Semenzato G, Pezzutto A, Agostini C, Albertin M, Gasparotto G
Clinica Medica 2, Via Giustiniani 2, Padova, Italy
Cancer; 48(10):2191-2197 1981

In the peripheral blood of patients with chronic B-cell lymphocytic leukemia (B-CLL) absolute numbers of E-rosetting lymphocytes were increased. The proportions of TG and TM cell subsets were analyzed, as were their effects on the pokeweed mitogen (PWM)-dependent differentiation of normal allogenic B cells of of autologous leukemic cells. The TG lymphocyte subset was further studied for its cytotoxic activity in antibody-dependent cellular cytotoxicity (ADCC). A marked increase both in percentages and in absolute numbers of TG cells was found. TM lymphocytes percentages were normal, but because of the T lymphocytosis occurring in all patients, the absolute numbers of TM were increased. TM and TG subsets showed helper and suppressor activity, respectively, in PWM-induced B-cell differentiation. TG cells displayed effector cell activity in ADCC. The results provide further evidence that T lymphocytes from patients with B-CLL are functionally normal. However, a noticeable increase of the T-cell subset having suppressor and cytotoxic activity in ADCC was observed. This may be the consequence of a normal immune reaction to the leukemic population. (Author abstract) (45 Refs)

13. LONG-TERM CULTURE OF NORMAL AND LEUKEMIA HUMAN BONE MARROW.

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Dept. Radiology, Cancer Biology Res. Lab., Stanford Univ. Medical Center, Stanford, CA, 94305
Haematol Blood Transfus; 26:276-288 1981

A method for the long-term culture of human marrow cell populations based on modifications of the murine system is presented. Normal marrow specimens from ribs of patients undergoing thoracotomy, aspirates of normal sternal marrow from patients undergoing cardiovascular surgery, and aspirates from the iliac crests of patients with acute myeloid leukemia (AML) before treatment, while in remission, and during relapse were cultured in Fisher's and McCoy's medium. Adipocyte-containing confluent stromal layers could be initiated and maintained for periods of at least 5 mo in either medium when supplemented with both horse serum (HoS) and hydrocortisone. Granulocyte-macrophage progenitor cells (CFUc) were supported for up to 12 wk in Fisher's growth medium supplemented with hydrocortisone and 25% HoS or 12.5% HoS and 12.5% fetal bovine serum (FBS), but the number of colony-forming cells recovered was usually less than 50 per 10(5) cells assayed. In contrast, McCoy's medium supplemented with both FBS and HoS contributed to significantly greater yields of CFUc. The results suggest that hematopoiesis in long-term liquid cultures of human marrow is dependent upon the presence of lipid-laden adipocytes. (27 Refs)

14. PROLIFERATION AND MATURATION OF HEMOPOIETIC CELLS IN ADULT PATIENTS WITH DIFFERENT FORMS OF ACUTE LEUKEMIA AND CHRONIC MYELOID LEUKEMIA IN AGAR AND LIQUID CULTURES.

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Haematol Blood Transfus; 26:251-254 1981

Of 183 patients studied 31 had acute lymphoblastic leukemia (ALL), [illegible] acute non-lymphoblastic leukemia (ANLL), 10 acute undifferentiated leukemia (AUL), 9 hematopoietic dysplasia (HD), 26 chronic myeloid leukemia - blast crisis (CML-BC), 43 chronic myeloid leukemia - chronic stage (CML-CS), 16 chronic myeloid leukemia - accelerated stage (CML-AS), 3 myelofibrosis - blast crisis (MMM-BC), and 72 were controls. CSF induced leukemic growth type response in 6% ALL, 67% ANLL, 50% AUL, and 56% HD. Of the 16 ANLL non-maturation patients, 6 had absolute arrest of blast cells maturation at level of blasts-promyelocytes and blasts-promonocytes in liquid cultures (LC). In 10 ANLL maturation patients blast cells possessed the ability to mature to monocytes-macrophages and/or immature granulocytes. ALL and AUL patients demonstrated intensive granulomonocytopoiesis in 7 day LC. Response to colony stimulating factor by CML patients in different stages was presented. (5 Refs)

15. INCREASED ASCORBIC ACID CONTENT IN CHRONIC LYMPHOCYTIC LEUKEMIA B LYMPHOCYTES.

Liebes L, Krigel R, Kuo S, Nevrla D, Pelle E, Silber R
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Proc Natl Acad Sci USA; 78(10):6481-6484 1981

Human lymphocyte extracts analyzed by high-performance liquid chromatography reveal a major UV-absorbing peak that was shown to be ascorbic acid by spectral, chemical, and enzymatic criteria. Because this peak appeared very prominent in the elution profile of chronic lymphocytic leukemia (CLL) lymphocyte extracts, we measured the ascorbic acid content in lymphocytes from the blood of normal subjects and untreated patients with chronic lymphocytic leukemia. A significantly higher concentration of 111 +-15.3 nmol per 10(8) cells (mean +- SEM) was found in CLL lymphocytes than in normal blood lymphocytes, which contained 42.2 +-3.3 nmol per 10(8) cells. Selective enrichment with B and T cells showed that this difference was limited to the chronic lymphocytic leukemia B cell, which had 5-to 15-fold higher content of ascorbic acid than normal B cells had. In contrast, the ascorbic acid level was similar in normal and CLL T cells. The very high ascorbic acid content provides the chronic lymphocytic leukemia B cell with a reducing substance that could react with oxidants or free radicals. (Author abstract) (29 Refs)

16. ADULT T-CELL LEUKEMIA: ANTIGEN IN AN ATL CELL LINE AND DETECTION OF ANTIBODIES TO THE ANTIGEN IN HUMAN SERA.

Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita KI, Shirakawa S, Miyoshi I
Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan
Proc Natl Acad Sci USA; 78(10):6476-6480 1981

Indirect immunofluorescence of certain human sera demonstrated an antigen(s) in the cytoplasm of 1-5% of the cells of a T-cell line, MT-1, from a patient with adult T-cell leukemia (ATL), which is endemic in southwestern Japan. The antigen was not detected in other human lymphoid cell lines, including six T-cell lines, seven B-cell lines, and four non-T non-B cell lines. The antigen did not show cross antigenicity with that of herpesviruses, including Epstein-Barr virus, herpes simplex virus, cytomegalovirus, varicella-zoster virus, herpesvirus saimiri, and Marek disease virus. The proportion of antigen-bearing cells was increased by a factor of approx five on culture in the presence of 5-iodo-2'-deoxyuridine. Antibodies against the antigen in MT-1 cells were found in all 44 patients with ATL examined and in 32 of 40 patients with malignant T-cell lymphomas (most of them had diseases similar to ATL except that leukemic cells were not found in the peripheral blood). The antibodies were also detected in 26% of the healthy adults examined from ATL-endemic areas but in only a few of those examined from ATL-non-endemic areas. On electron microscopy, extracellular Type C virus particles were detected in pelleted MT-1 cells cultured in the presence of 5-iodo-2'-deoxyuridine. (Author abstract) (26 Refs)

17. A CRITICAL REVIEW OF THE LITERATURE ON HAIRY CELL LEUKEMIA. FIRST PART: DIAGNOSIS AND PROGRESSION.

Bernadou A
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Sem Hop Paris; 57(33-36):1366-1371 1981

Hairy cell leukemia (HCL) affects primarily men between 19 and 87 yr old with a median age of 53 yr. In 75% of cases, splenomegaly is associated with HCL. Cytopenias have been observed in 45-90% of patients with HCL. Other associated anomalies include the presence of a circulating mononuclear clear cell, myelofibrosis and leukemic infiltration of the bone marrow. Tartrate resistant acid phosphatase activity is diagnostic for HCL. Although the number of B and T lymphocytes are decreased in HCL, there does not seem to be any profound problems with humoral or cellular immunity. The diagnosis of HCL is often difficult. Medullary biopsy is the only test that is reliable in 70% of cases. Because of the associated neutropenia, the principal risk of HCL is infection. The cytopenia associated with HCL can often be successfully controlled with surgical treatment. Splenectomy has improved the median survival rate and the infectious risk in patients with HCL. The postoperative mortality rate has reached 15% following splenectomy for HCL. Other treatments used include symptomatic therapy, chemotherapy, and leukapheresis. (134 Refs) (In FRE)

18. PROLYMPHOCYTIC LEUKEMIA.

Ralfkiaer E, Plesner T, Hansen MM, Andersen C, Hou-Jensen K
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Ugeskr Laeger; 143(37):2339-2343 1981

Recent studies on prolymphocytic leukemia (PLL) are reviewed. In a series of 53 patients, there were 32 men and 21 women (40-87 yr old, median age 67 yr). Splenomegaly was found in 53/53 cases, hepatomegaly in 25/53, lymph node involvement in 10/53, skin infiltration in 8/53, lymphocytosis in 53/53, anemia in 50/50, and thrombocytopenia in 31/50. The immunological characteristics were investigated in 34 patients: B-cell markers were found 23/34 cases, T-cell markers in 10/34, and both B- and T-cell markers in 1/34. Dominance of prolymphocytes with typical nuclear structure in the blood and bone marrow is characteristic of PLL. The cases derived from B lymphocytes appear to be related immunologically to non-Hodgkin's lymphoma, and the B prolymphocyte can be differentiated immunologically from the lymphocyte of B-cell chronic lymphocytic leukemia. The survival of the patients is short, ranging from wk to mo, and the patients do not respond to the current therapy for chronic lymphocytic leukemia. The best therapeutic results to date are achieved by splenectomy combined with leukapheresis or polychemotherapy as employed in non-Hodgkin's lymphoma. (28 Refs) (In DAN)

19. PH(1)-NEGATIVE T LYMPHOCYTIC COLONIES IN AGAR CULTURES OF PERIPHERAL BLOOD IN CHRONIC MYELOID LEUKEMIA.

Bagnara GP, Biagini G, Marani M, Bonsi L, Severi B, Valvassori L, Comis M, Nobile F, Iacopino P, Ronco F, Neri A
Instituti di Isotologia ed Embriologia Generale e, Universita di Bologna, Italia
Acta Haematol (Basel); 66(3):174-180 1981

T lymphocytic colony formation by peripheral lymphocytes separated by discontinuous albumin gradient centrifugation was evaluated in eight patients with Philadelphia (Ph(1))-positive chronic myeloid leukemia (CML). Colonies were obtained using a liquid-on-agar culture system recently introduced (PHA overlayer-WBC feeder layer assay) which has been shown to be simple and reliable. The pattern of colony growth in CML and in normal controls was similar, the peak ranging from the 4th to the 6th day. Also the morphological aspects of colonies did not differ in the two groups. Cells recovered from CML lymphocytic colonies were shown to belong to T cell lineage, as they are able to form spontaneous E-rosettes and to respond to mitogenic stimulation in vitro. In contrast, cells recovered from all other cultured fractions failed to display these properties. Cytogenetic analysis showed that T colony cells were Ph(1)-negative whereas the chromosome anomaly was found in nonlymphoid colonies of the same patients, thus suggesting a nonclonal origin of T lymphocytes in CML. (Author abstract) (25 Refs)

20. CONSIDERATIONS ABOUT THE USE OF LEVAMISOLE IN PATIENTS AFFECTED BY PRIMARY CANCER.

Marzo C, Gnasso P, Gennarelli E, Vitiello N, Borrelli G, Pasquinucci S, Antropoli L
Istituto di Clinica Tisiologica, I Facolta di Medicina e Chirurgia dell'Universita degli Studi di Napoli, Napoli, Italy
Rass Int Clin Ter; 61(5):289-293 1981

This study was undertaken to elucidate some aspects of levamisole (Le) effect on primary lung cancer. Advantageous and undesirable side effects were studied. All 51 patients with lung cancer diagnosis had tests in vivo for recall antigen (paraphenylenediamine - PPD), and in vitro for rosettes (E, EA, EAC), and lymphocyte blast (phytohemagglutinin - PHA). These tests were repeated every 21-28 days. There was not always agreement between tests in vivo and in vitro. Patients were treated by surgery, irradiation, and cytostatic therapy. Le therapy was started when percent of lymphocytes forming rosettes E in vitro was less than 50%, even in cases when PPD was highly positive (ie giving normal reaction). Of the 51 patients 16 were immuno depressed at the time of diagnosis. All 16 patients received Le therapy. Another seven became immuno depressed later (5 after cytostatic therapy, which did not change PPD results). In all 23 patients, Le therapy caused almost immediate return to normal for rosette forming lymphocyte numbers. Patients showing reduction of lymphocytes T and decrease in tuberculine sensitivity, after Le therapy, demonstrated increase in T lymphocytes and no change in tuberculine (contrary to other published data). Le therapy did not show any side effects. Possible explanation of these results was offered. (11 Refs) (In ITA)

21. ALTERATIONS OF PERIPHERAL BLOOD B-LYMPHOCYTE POPULATIONS IN PLASMA CELL DISORDERS.

Dillman RO, Royston I, Meserve BL, Griffiths JC
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Cancer; 48(10):2211-2217 1981

Peripheral blood lymphocytes of patients with multiple myeloma, macroglobulinemia, and monoclonal gammopathy of uncertain significance were analyzed for B cells, and cells bearing kappa light chains and lambda light chains on their surfaces. Compared with controls, the number of B cells were decreased in all three groups. Contrary to other reports, the authors found a B-cell depression of similar magnitude in patients with untreated myeloma and in those with apparently benign monoclonal gammopathy. There was no difference between treated and untreated myeloma patients as a group, or as individuals studied before and after treatment. However, in comparison to control patients, alkylator therapy depressed the WBC count, lymphocyte count, and B-cell number both in the myeloma and in the macroglobulinemia groups. All five patients with previously untreated macroglobulinemia had an increased proportion of circulating lymphocytes with surface light chains of the same type as the M protein. Two patients with IgG myeloma-like disorders had increased circulating B cells with monoclonal surface light chains. This study supports the concepts that normal B cells are depressed in plasma cell disorders, and that abnormal B cells, which are apparently monoclonal, do circulate in some cases. Our results are compared with other published data. (Author abstract) (38 Refs)

22. EFFECT OF MAINTENANCE MOPP/COPP TREATMENT ON THE NUMBER OF FUNCTIONS OF LYMPHOCYTES T AND B IN THE PERIPHERAL BLOOD OF PATIENTS WITH HODGKIN'S DISEASE DURING REMISSION.

Pluzanska A, Kaluzna W
Osrodek Onkologii, Oddzial Chemioterapii, ul Gagarina 4, Lodz, Poland
Pol Arch Med Wewn; 65(6):475-481 1981

T and B lymphocytes in peripheral blood were studied in patients with Hodgkin's disease who experienced remission with MOPP/COPP. During this study, some patients were continued on drug therapy while a second group received no treatment. In both groups a functional defect of lymphocytes was demonstrated compared to healthy controls. Patients showed impairment of blastic transformation after challenge by mitogens and increase of anergy in skin tests. In the group on continued maintenance therapy T and B counts were decreased. (14 Refs) (In POL)

23. TUMOR PROMOTER PHORBOL MYRISTIC ACETATE STIMULATES IMMUNOGLOBULIN SECRETION CORRELATED WITH GROWTH CESSATION IN HUMAN B LYMPHOCYTE CELL LINES.

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J Clin Invest; 68(4):1093-1096 1981

Ig production by lymphoblast cell lines was studied using protein A-RBC plaque formation to detect individual secreting cells. Ig secretion by 6 of 12 human B-cell lines tested could be stimulated up to 20-fold by phorbol myristic acetate (PMA) at subtoxic concentrations of 10-1,000 ng/ml depending on the line. Stimulation was found with both IgM and IgG cell lines. No switch of Ig class synthesis was found in the cell lines as a result of PMA incubation. Increase in Ig secretion was closely associated with cessation of growth resembling induction of terminal differentiation in the cells. PMA induction of Ig secretion in B lymphocytes from normal peripheral blood requires the cooperation of T cells. PMA stimulation of certain cell lines reported here suggests that the lines are late in the differentiation pathway to plasmacyte and can be easily triggered to secrete Ig by membrane-altering agents. (Author abstract) (27 Refs)

24. STUDIES ON BLOOD LYMPHOCYTES OF PATIENTS WITH NODULAR POORLY DIFFERENTIATED LYMPHOCYTIC LYMPHOMA.

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J Clin Pathol; 34(8):896-901 1981

T and B lymphocytes were measured in pretreatment blood samples from patients with nodular poorly differentiated lymphocytic lymphoma (NPDLL). There were significant differences in T cell values between control groups and patients with NPDLL. In 13 out of 20 cases of NPDLL blood lymphocytes showed abnormalities of Ig light chain expression and were considered to show an abnormal clonal expansion of B lymphocytes. The abnormal clone of B cells in the blood reflected that found in lymph nodes and could be detected in the absence of bone marrow involvement or blood lymphocytosis. (Author abstract) (17 Refs)

25. LONGITUDINAL STUDIES OF BLOOD LYMPHOCYTE CAPACITY IN HODGKIN'S DISEASE.

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Cancer; 48(9):2010-2015 1981

Blood lymphocyte functional capacity and serum Ig were studied in 40 patients with Hodgkin's disease (HD) admitted to Radiumhemmet, Stockholm, before treatment and in complete remission 2-56 mo following termination of radiotherapy (total nodal irradiation [TNI]; n = 29) or chemotherapy (MOPP: n = 11). Lymphocyte studies included determination of total lymphocyte and T-cell counts and evaluation of spontaneous DNA synthesis during the first day of culture and mitogen- (concanavalin A, pokeweed mitogen) and antigen (purified protein derivative, PPD)-induced activation on the 3rd day. Blood lymphocyte and T-cell counts decreased dramatically following TNI. A slow restitution was seen, but pretreatment levels were not reached even 4 yr following therapy. The responses to ConA and PPD but not PWM were significantly reduced shortly after TNI. The mitogen response did not increase with time as did the PPD response. Lymphocyte counts and lymphocyte stimulation, which were severely depressed before treatment of patients in the chemotherapy group, remained unchanged 2-36 mo after termination of therapy. A significant reduction of IgM levels was observed regardless of the mode of treatment. Splenectomy prevented the profound reduction of blood lymphocyte and T-cell counts following therapy but did not influence the other immunologic variables under study. (Author abstract) (43 Refs)

26. HUMAN THYMOMA: IMMUNOLOGIC CHARACTERISTICS OF THE LYMPHOCYTIC COMPONENT.

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Cancer; 48(9):1992-1995 1981

Several immunologic parameters were investigated in the lymphocytic component of 10 thymomas, characterized by a variable degree of lymphocytic infiltration. The majority of thymoma lympho cytes are T-cell in nature, as are lymphocytes from the normal thymus. Lymphocytes from six thymomas with moderate or predominant lymphocytic infiltrates were capable of forming stable E-rosettes, (mean percentage +- SD: 78.0 +-5.2); binding peanut agglutinin (67.3 +-8.6); and exhibiting receptor for the Fc-portion of IgM (21.8 +-6.0) at percentages that were close to those found in the normal thymus. On the other hand, lower numbers of stable E-rosetting cells (26.8 +-8.7), FNA-positive cells (27.5 +-12.4), and remarkably higher percentages of cells with receptors for IgM (54.0 +-4.2) were demonstrated by the lymphocytic population of four thymomas with scant lymphocyte components. In addition, lymphocytes from tumors with scant lymphocyte components show a higher proliferative response to phytomitogen (PHA), therefore exhibiting immunologic features comparable to those of the more mature pool of normal medullary thymocytes. The observed immunologic similarities between the populations of lymphocytes from thymomas and from the normal thymus gland suggest an exclusively epithelial origin of the thymoma. (Author abstract) (22 Refs)

27. ANALYSIS OF THE TRANSFORMATION OF HUMAN LYMPHOCYTES BY EPSTEIN-BARR VIRUS III. INDUCTION OF EARLY EVENTS BY P3HR-1 STRAIN WITHOUT SUBSEQUENT IMMORTALIZATION.

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Med Microbiol Immunol (Berl); 170(1):19-26 1981

The interaction between Epstein Barr virus (EBV) derived from P3HR-1 cell line and human cord blood lymphocytes was studied by simultaneous observations of events occurring in EBV-induced transformation in individual cells. EBV derived from B95-8 cells (B95-8 EBV) was used for positive control. B95-8 EBV induced a complete series of early transformation events including nuclear antigen (EBNA) and DNA synthesis and blastogenesis, followed by immortalization of the infected lymphocytes. When the same cord preparation was exposed to P3HR-1 EBV, EBNA-positive cells were clearly identified even 12 hr after viral exposure and reached a max of 31% at 24 hr, followed by a plateau for a subsequent 24 hr. In contrast to B95-8 EBV infection, EBNA staining was weak. At 24 hr, blastogenesis was also significant while 3H-thymidine incorporation was not. In addition to weak fluorescence, brilliant EBNA staining later occurred at 48 hr and reached about 20% of the total positive cells on day 5. The EBNA-positive blast cells then became grain-positive at 36 hr and the immunofluorescent cells reached 61.1% at 120 hr. At this time, nearly 50% of the stained nuclei showed evidence of DNA synthesis. At 72 hr, all examined mitotic cells were positive for EBNA and the mitotic frequency was as high as that seen in B95-8 EBV infections. Characteristic cell aggregates were also seen. The number of infected cells decreased gradually after 1 wk and degenerated in about 2 wk. Essentially the same results were obtained, using different stocks of EBV derived from both P3HR-1 sublines A and B and different cord cell preparations. The results indicated that P3HR-1 virus does retain early transforming functions for primary human B lymphocytes, although infected cells have a short life span. (28 Refs)

28. CHARACTERIZATION OF THE PHYTOHEMAGGLUTININ-INDUCED PROLIFERATING LYMPHOCYTE SUBPOPULATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS USING A CLONOGENIC AGAR TECHNIQUE AND MONOCLONAL ANTIBODIES.

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Blood; 58(5):1053-1055 1981

Peripheral blood lymphocytes from normal donors and patients with chronic lymphocytic leukemia, B-cell type, were purified into T, helper T, and suppressor T lymphocytes by fluorescence-activated cell sorting using OKT3, OKT4, and OKT8 monoclonal antibodies. The max response of the purified subpopulations to stimulation by phytohemagglutinin (PHA) was determined by measuring the production of colonies when the stimulated cells were grown on agar. The helper T cells in normal and CLL patients were the most responsive to PHA stimulation, although the responsiveness of helper T cells to PHA was decreased in CLL. Purified CLL B cells responded minimally to PHA stimulation, but normal B lymphocytes did not. The abnormal response of CLL lymphocytes to PHA appears to be due to abnormal helper T cells, and, to a smaller extent, to the ability of CLL B lymphocytes to respond. (Author abstract) (17 Refs)

29. PURINE NUCLEOSIDE PHOSPHORYLASE (PNP) AND ADENOSINE DEAMINASE (ADA) ACTIVITIES EXAMINED CYTOCHEMICALLY IN UNFIXED LYMPHOCYTES OF PATIENTS WITH LYMPHOPROLIFERATIVE DISORDERS.

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Blood; 58(5):897-903 1981

New techniques have been devised for the cytochemical demonstration of purine nucleoside phosphorylase (PNP) and adenosine deaminase (ADA) activities in unfixed human lymphocytes. A suspension of living lymphocytes is mixed with agarose soln containing the reagents for the detection of PNP or ADA activity on a glass slide. The mixture solidifies, is incubated, and then dried for light-microscopic observation. Reactive cells are recognized by the diffusely deposited granules of formazan, the end-product of the cytochemical reaction, and are divided into three groups of the cell with the low, middle, and high enzyme activity by the number of the granule. In healthy adults, the mean percentages of PNP- and ADA-positive cells were more than 90% in unfractionated lymphocytes, T-cell fractions, and complement-receptor cell fractions and cells with middle PNP and ADA activities were predominant. The PNP and ADA staining was observed in lymphoid cells of patients with lymphoproliferative disorders. A decrease in the percentage of PNP-positive cells concomitant with a relative increase of cells with the low enzyme activity was observed in the lymphocytes of nine patients with chronic lymphocytic leukemia (CLL). Similar findings were obtained in the ADA staining of the lymphocytes of five patients with B-cell CLL. (Author abstract) (31 Refs)

30. IMMUNOLOGICAL STUDIES IN CHRONIC LYMPHOCYTIC LEUKEMIA. II. NATURAL KILLER- AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY POTENTIALS OF MALIGNANT AND NON-MALIGNANT LYMPHOCYTE SUBSETS AND THE EFFECT OF ALPHA-INTERFERON.

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Leuk Res; 5(4/5):349-355 1981

The effector cell potential of chronic lymphocytic leukemia (CLL) subsets was determined in the natural killer (NK) and antibody-dependent cellular cytotoxicity (ADCC) assays. Lymphocyte subpopulations were isolated from peripheral blood obtained from 25 (43-76 yr old) CLL patients. The behavior of CLL cells in NK and ADCC assays was determined. Basic experimental conditions for the assays were determined. When unseparated lymphocytes from CLL patients were tested in NK (21 patients) and ADCC (25 patients) assays and compared to the cytotoxicities of 20 normal donors, the CLL cells were defective in both tests. The behavior of CLL cells in NK assays was defective with or without 1,000 IU alpha-interferon (AIF). The NK and ADCC defects were found mainly in the non-T fraction, while the T cells exhibited subnormal levels of lysis. By depleting the non-T cells of mouse rosette forming cells, a null cell subset was purified that exhibited considerable lysis in the NK test. AIF did not enhance ADCC by unfractionated CLL cells. When the NK activity of three CLL patients were tested against 7 target cell lines with NK sensitivities in normal donors ranging from very low to extremely, the same pattern was retained in the patients, although the addition of AIF tended to diminish the tendency by boosting the NK activity against the resistant lines proportionately more than against the sensitive ones. Compared with lysis by cells from normal donors, the lysis of cells from the patients, was still defective with all cell lines tested. (19 Refs)

31. CHARACTERISTICS AND ACTION OF THE CONCANAVALIN A (CON A)-INDUCED SUPPRESSOR CELLS IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES.

Toge T, Yanagawa E, Nakanishi K, Kohno H, Yamada Y, Hattori T
Dept. Surgery, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi, Hiroshima 734, Japan
Gan To Kagaku Ryoho; 8(5):802-808 1981

After treatment with Con A, peripheral blood lymphocytes from both normal donors and cancer patients contained Con A-induced suppressor cells which depress the proliferative respons e of lymphocytes from normal donors. Con A-induced suppressor cells were present among E-rosette forming cells. The activities of these cells were apparent when added on day 0 of responder cell cultures. In our assay system, allo-antigen-induced proliferation as well as mitogen-induced proliferation was depressed by Con A-activated cells. In esophageal, colorectal and gastric cancer patients, a significant increase in Con A-induced suppressor cell activity as compared with normal donors was observed, whereas in patients with breast cancer, there was no such increase in activity. In patients with advanced gastric cancer, increased suppressor cell activity was also found, and it decreased significantly after resection of the tumors. The suppressor mechanisms may be of major importance in governing the outcome of antitumor responses. (25 Refs) (In JPN)

32. EFFECT OF LEVAMISOLE ANALOGS ON E-ROSETTE FORMATION BY MITOMYCIN C-TREATED HUMAN LYMPHOCYTES.

Koseki K, Akaza H, Hara T, Kobayashi K, Umeda T, Niijima T, Iwaguchi T
Dept. Urology, Faculty Medicine, Univ. Tokyo, Bunkyu-ku, Tokyo 113, Japan
Gan To Kagaku Ryoho; 8(5):790-795 1981

Incubation of lymphocytes in mitomycin C (MMC) reduced E-rosette formation by human T-lymphocytes, which indicates a possible immunological disadvantage to cancer patients treated by chemotherapy. We investigated whether or not levamisole, known to be a nonspecific immunopotentiator, and its analogs show an E-rosette-restorative effect on the MMC-treated lymphocytes. Levamisole and its analogs, dexamisole, tetramisole, phenylimidazothiazole and paraaminolevamisole, were used at a concentration of 40 ug/ml. When lymphocytes from healthy donors were incubated with MMC (0.01 ug/ml, 0.1 ug/ml, 1.0 ug/ml) for 60 min at 37 C, the rates of E-rosette formation were reduced from 67% to 50, 48, and 43%, respectively. However, when levamisole and its analogs were added to the medium, the percentages of E-rosette formation were higher than those of lymphocytes incubated with MMC alone. Paraaminolevamisole was the most effective in preserving E-rosette formation. Our results indicate that levamisole and its analogs might restore, in cancer patients, the secondary cellular immunity reduced by cancer chemotherapeutic agents. (15 Refs) (In JPN)

33. LYMPHOBLASTIC LYMPHOMA IN CHILDREN: THEIR RECOGNIZABILITY AS T- OR B-CELL NEOPLASMS IN HISTOLOGICAL SLIDES (ROUTINE SECTIONS).

Schwarze EW, Pileri S, Tolksdorf G, Kampert-Blumberg J
Institut fur Pathologie der Universitat, Hospitalstrasse 42, D-2300 Kiel, W. Germany
Klin Paediatr; 193(3):131-136 1981

A blind study was made of sections from tumor and lymph node biopsy material from patients with confirmed lymphoblastic lymphoma (lb L). Sixty patients included 51 children, one of whom had a virologically confirmed Burkitt's tumor. Routine serial sections were stained with hematoxylin-eosin and Giemsa stain, Gomori silver stain, or PAS-reaction. Of 20 cases diagnosed by immunologic, cytochemical, or virological analysis as T-, B-, or non-T/non-B lb L, 18 were correctly diagnosed by histological examination alone. Histological diagnosis matched definitive diagnosis in 48 of 51 children. T-cell lb L was characterized by equal complete and partial lymph node involvement, a high frequency of diffuse infiltration, few reticular fibers, and epithelioid venules in 50% of cases. B-cell lb L was characterized by 75% complete lymph node involvement, diffuse and nodular infiltration in 40% of cases, collagenous fibers in 55%, infiltrate necrosis in 65%, 'starry-sky' macrophages in 85%, and eosinophils in 30%. Intracellular structure and staining for acid phosphates also were of diagnostic significance. (36 Refs) (In GER)

34. PWM-INDUCED GENERATION OF IMMUNOGLOBULIN-SECRETING CELLS IN PATIENTS WITH MULTIPLE MYELOMA.

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Klin Wochenschr; 59(19):1101-1108 1981

The pokeweed-mitogen-induced transformation of B-lymphocytes into Ig-secreting cells was studied in vitro in 25 patients with multiple myeloma using a reverse hemolytic plaque assay. Fifteen patients showed a good response in generating Ig-secreting cells, whereas 10 patients showed a decreased B cell reactivity which was not due to intermittent melphalan/steroid therapy administered to 15 patients. Experiments with lymphocyte subpopulations demonstrated that the inability of some multiple-myeloma patients to generate Ig-secreting cells was always based on a defect in the B-cell subset. Co-culture experiments with lymphocytes from normal individuals and patients revealed a cell-mediated suppression in one case, whereas humoral suppressive factors in the patients' serum could not be observed using the reverse hemolytic plaque assay. Patients were classified into three groups: (a) patients with a normal B-cell function, (b) patients with a reversible, tumor-dependent suppression of B-cell reactivity and (c) patients in whom the normal B-cell population was replaced by non-reactive cells. (Author abstract) (52 Refs)

35. HISTOLOGICAL CLASSIFICATION OF MALIGNANT LYMPHOMAS AND ITS PROGNOSTIC SIGNIFICANCE.

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Ther Umsch; 38(9):845-853 1981

The histological classifications of Hodgkin's disease (HD) and of non-Hodgkin's lymphoma (NHL) and their prognostic significance are reviewed. The various classifications differ from one another chiefly due to a considerable divergence regarding the use of morphological and/or functional parameters. Among the NHL, large-cell lymphocytic lymphomas usually have a large proliferating fraction compared with the small-cell type. Consequently, the evaluation of the cell size yields information on the probable growth behavior of NHL. The probable generalization pattern of the cell population can also be predicted from the cell size at least in the case of certain B-cell NHL. NHL with nodular components have a better prognosis even without therapy than NHL with diffuse growth pattern. In the case of HD, there is a correlation between the histological subtype and stage of the disease. Patients with more unfavorable variants of HD, such as lymphocyte-depleted or mixed cellular types, are usually in a more advanced stage at the time of diagnosis than patients with histologically more favorable types. The prognostic significance of the subtypes of HD has been diminished by improved therapy. (24 Refs) (In GER)

36. MALIGNANT SKIN LYMPHOMA: OLD HYPOTHESES AND RECENT CONCEPTS.

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MMW; 123(35):1291-1296 1981

The recent development of new concepts in cutaneous malignant lymphoma is reviewed. Malignant reticulopathies according to the old terminology are now classified as cutaneous T-cell and B-cell lymphoma, cutaneous leukemia (lymphocytic, myelocytic, and monocytic leukemias), cutaneous histiocytoses, and cutaneous Hodgkin's disease. The frequency of cutaneous non-Hodgkin's lymphomas of low-grade and high-grade malignancy was studied on the basis of three different series. Among the non-Hodgkin's lymphomas of low-grade malignancy, mycosis fungoides accounted for 20-30%, Sezary's syndrome for 4-9%, B-cell type chronic lymphocytic leukemia (CLL) for 0.3-16%, T-cell type CLL for 0.7-3%, immunocytoma for 6-22%, centrocytic lymphoma for 5-9%, and centroblastic-centrocytic lymphoma for 1.5-13%. Among the unclassified and high-grade cutaneous non-Hodgkin's lymphomas, centroblastic lymphoma accounted for 1.5-6%, immunoblastic lymphoma for 4-12%, lymphoblastic lymphoma for 3-8%, and unclassified lymphoma for 10-16%. (no Refs) (In GER)

37. ANTIBODIES IN HUMAN SERA REACTIVE AGAINST AN INTERNAL STRUCTURAL PROTEIN OF HUMAN T-CELL LYMPHOMA VIRUS.

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Nature; 294(5838):271-273 1981

A limited survey was designed to determine whether natural antibodies reactive against the human retrovirus isolate, HTLV, can be detected in human sera. The assay involved use of a radioimmune precipitation of 125I-labeled HTLV-cr p24 by human sera using a double antibody system. The p24 of HTLV-cr was purified to homogeneity from density-banded virus and radiolabeled with 125I. Serum from pat ient CR (the source of the isolate) and serum from another patient, MJ, with Sezary syndrome showed high reactivity to HTLV-cr p24. Twenty-one sera from various T-cell malignancies and 50 sera from random normal donors showed no significant precipitating activity. Eleven sera from close family members of patients with T-cell malignancies and previous evidence of HTLV infection were studied. Only one, from the wife of patient CR, reacted strongly in the immunoprecipitation. The antibodies against p24 are present in human sera, and these are specifically directed at HTLV-cr proteins and not at cell-specific determinants. Thus, the immunological reactions are not those reported in human sera against animal virus glycoproteins which, lacking virus specificity, are directed against the carbohydrate residues of the glycoprotein. The antibodies against HTLV are thus the first evidence for a specific immune response in humans against a retrovirus. (15 Refs)

38. PHENOTYPIC HETEROGENEITY AND CELLULAR ORIGINS OF T CELL MALIGNANCIES.

Greaves MF, Rao J, Hariri G, Verbi W, Catovsky D, Kung P, Goldstein G
Membrane Immunology Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Leuk Res; 5(4/5):281-299 1981

The reactivity of the OKT series of monoclonal antibodies was compared with a panel of other monoclonal antibodies, sheep erythrocyte rosette formation, and expression of terminal deoxynucleotidyl transferase in untreated T cell malignancies. Also included in the series were OKT11 and OKT11A, two new monoclonal antibodies with pan-T activity. The composite phenotypes of cells from individual patients were classified according to a presumptive sequence of T lymphocyte differentiation. Six categories of T cell phenotypes were designated, four of thymic type and two of mature T cells. Cells from 82 untreated patients with T cell malignancy were tested with the OKT series of monoclonals and other markers. The OKT defined phenotype of 13 established T cell lines is presented. The most striking result from this analysis was the association between overall phenotype and diagnostic subgroup of T cell malignancy. The results indicated that T cell leukemias have exclusive, composite phenotypes which are in themselves remarkably heterogeneous. It was suggested that T-cell acute lymphoblastic leukemia and T-cell non-Hodgkin's lymphoma in young patients originate in a thymic stem cell with varying levels of maturation arrest, whereas those T malignancies in adults with a mature T cell phenotype arise from long-lived immunocompetent T cells. (79 Refs)

39. STUDIES ON T CELL BEARING FC RECEPTORS FOR IGG OF PERIPHERAL LYMPHOCYTES IN PATIENTS WITH BLADDER CARCINOMA.

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Dept. Urology, Kobe Univ. Sch. Medicine, Kobe, Japan
Hinyokika Kiyo; 27(6):637-647 1981

To test the cellular immunocompetence in patients with bladder carcinoma, a study was made on the lymphocyte subpopulation of 34 patients and 35 healthy men. T cell was identified by spontaneous rosette formation with sheep RBC, and B cell was identified by EAC rosette formation. T lymphocytes bearing Fc receptors for IgG (IgGFcR+ T cells) were detected by double rosette formation of neuraminidase treated sheep RBC and glutaraldehyde treated sensitized ox RBC. The percentages of IgGFcR+ T cells in total T cells in peripheral lymphocytes of 35 healthy men and 34 untreated bladder cancer patients were 5.8 +-1.9% and 14.2 +-8.4% respectively, the percentages of T cells in peripheral lymphocytes of 35 healthy men and 34 untreated bladder cancer patients were 81.3 +-6.3% and 68.6 +-14.0% respectively. The difference between these figures was statistically significant. There was a tendency to decrease in percentage and absolute count of T cells in the patients with higher grade and stage of the tumor. Contrary, there was a tendency to increase percentages of IgGFcR+ T cells in total T cells of the patients with higher grade and stage of the tumor. No influence of operation was found on T cell percentage, absolute count of T cell and the percentage of IgGFcR+ T cells in total T cells. Steroids which were secreted by stimulation of operative stress might have an effect on the percentages of IgGFcR+ T cells in total T cells. (Author abstract) (33 Refs) (In JPN)

40. IMMUNODEFICIENCIES IN HODGKIN'S DISEASE. PART I: T CELL-MEDIATED IMMUNITY.

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Clinical Immunology Service, Sloan-Kettering Inst., New York, NY
Clin Bull; 11(2):58-65 1981

The association between Hodgkin's disease and immunodeficiency states is reviewed. Immunodeficiencies may predispose patients with Hodgkin's disease to a second neoplasm and to increased risk of infectious complications, especially viral and fungal (eg herpes zoster and cryptococcosis). Both in vivo and in vitro T cell-mediated immune responses in patients with various stages of Hodgkin's disease are discussed, including delayed type hypersensitivity, homograft rejection, lymphocyte response to soluble antigens and to mitogens and allo-antigens, analysis of T cells and T cell subsets, and cytotoxic response and mechanisms responsible for T cell-mediated immunodeficiencies. The role played by splenectomy in treatment of Hodgkin's disease is discussed. (71 Refs)

41. POSSIBLE CELLULAR IMMUNITY AGAINST ACOUSTIC NEUROMA.

Rasmussen N, Thomsen J, Tos M
Univ. ENT Dept., Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
Acta Otolaryngol (Stockh); 92(3/4):337-341 1981

Leukocyte migration capillary tube technique (LMCT) was used on WBC from 11 patients prior to acoustic neuroma surgery and 16 healthy control persons. The LMCT was carried out against acoustic neuroma extract, produced prior to the study, the with use of normal temporal lobe extract as control antigen. Four patients and one control person exhibited consistent cell-mediated immunity (CMI) against acoustic neuromas. The method is of no diagnostic value, but the results are sufficiently spectacular to merit further research. (Author abstract) (9 Refs)

42. POSSIBILITY OF IMMUNOSTIMULATION IN LUNG CANCER - STUDY OF LYMPHOCYTE SUBPOPULATIONS.

Battista P, Pistone C, Di Perna S, Colamartino P, Di Primio E, Robino A, Sacco C
Istituto di Patologia Generale, Universita di Chieti, Chieti, Italy
Boll Soc Ital Biol Sper; 57(11):1242-1246 1981

Bronchogenic cancer patients were evaluated before surgery and antiblastic therapy, also for possible future immunotherapy. Before any therapy all patients had rosette Et, Ea, and EAC tests. Tests were repeated after 3 days of levamisole (150 mg/day) treatment, followed immediately by surgery, and 3 days after surgery, too. Controls were 15 healthy persons. Percent rosette values were reported. Control rosettes were: 78% +-3% Et, 28% +-3% Ea, and EAC 12% +-3%. Before levamisole treatment rosettes were: 67.5% Et, 19.6% Ea, and 22.7% EAChu in lung cancer patients. After levamisole treatment they were: 71.5%, 24.5%, and 20.3% respectively. After surgery they were: 71.6%, 24.6%, and 25%, almost unchanged. After surgery rosette Ts were also determined and their value was 4%. Et and Ea rosettes were decreased and EAChu almost normal before levamisole treatment. After levamisole treatment the values were almost normal and they did not change after surgery, except for rather decreased Ts values. Such Ts decrease could be related in lung cancer patients to inhibitors or facilitators, which limit cell mediated immunological activity, through Ts inhibition. (4 Refs) (In ITA)

43. EPIDEMIOLOGIC, ETIOLOGIC AND IMMUNOLOGIC ASPECTS OF NASOPHARYNGEAL CARCINOMA (NPC).

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J Med; 12(4):257-284 1981

Epidemiologic studies indicate that mainland Chinese, especially those living in the South-East provinces, and overseas Chinese have the highest incidence of nasopharyngeal carcinoma (NPC) in the world. Most of the NPCs in this high-risk population are squamous cell carcinomas. Genetic and environmental factors implicated in NPC etiology are discussed, including HLA profiles, a putative second locus antigen (Sin-2) found in high-risk Chinese, environmental carcinogens, and vitamin A deficiency. Evidence for the role of Epstein-Barr virus (EBV) in NPC is presented. NPC patients have high antibody titers against all EBV antigens, and viral DNA has been detected in NPC epithelial cells. Early EBV infections may increase the likelihood of lymphocyte EBV induction and activation by environmental factors. (110 Refs)

44. RELATIONSHIP OF LEUKOCYTE NUMBERS, IMMUNOREGULATORY CELL FUNCTION, AND PHYTOHEMAGGLUTININ RESPONSIVENESS IN CANCER PATIENTS.

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JNCI; 67(4):809-814 1981

WBC were quantitated in peripheral blood from 35 solid-tumor cancer patients and related to levels of phytohemagglutinin (PHA)-induced DNA synthesis. Levels of glass-adherent, indomethacin-sensitive, or 24-hr preculture-sensitive immunoregulatory activity were evaluated in PHA-stimulated peripheral blood mononuclear cells (PBMC). Cancer patients and patients with depressed PHA responses had significantly greater monocyte percentages in their PBMC than did healthy subjects; patients with normal PHA responses did not. Patients with disseminated disease had significantly greater monocyte percentages and depressed T-cell percentages than did controls; patients with at most minimum residual disease did not. When monocyte and lymphocyte percentages were correlated by linear regression analysis to PHA responsiveness, no significant correlation was found. A highly significant negative correlation was noted between PHA responsiveness and levels of immunoregulatory cell function. Abnormal immunoregulatory function, apart from alterations in peripheral blood WBC percentages and numbers, contributes to impaired T-cell function in cancer patients. (Author abstract) (19 Refs)

45. HUMAN INTERFERONS - FEATURES AND CHANCES.

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Wien Klin Wochenschr; 93(14):439-457 1981

Interferons are soluble cellular products secreted by vertebrate cells in response to a wide variety of inducers. They confer resistance against many different viruses, inhibit proliferation of normal and malignant cells, impede multiplication of intracellular parasites, enhance macrophage and granulocyte phagocytosis, augment natural killer cell activity, and show several other immunomodulatory functions. In viral infections, interferon controls the spread of viruses by inhibiting viral protein synthesis and/or nucleic acid replication and by activating cellular immune responses which effectively eliminate virus-infected cells. Immune interferon, produced in a cellular immune response as the result of an infection, tumor, or hypersensitivity reaction, governs the local immune response to the abrogation of that tumor or other injury by directly reducing cell multiplication and recruiting cytotoxic cells. Clinical trials have shown some effectiveness of interferon in the treatment of chronic viral infections as well as some possible antitumor effects. Because of the extreme scarcity of human interf eron and the use of highly impure preparations, the results to date are not conclusive. Therapeutic effectiveness rather than prophylactic effects, has still to be proved by controlled clinical studies with purified interferon under economically feasible conditions. (Author abstract) (157 Refs) (In GER)

46. THE SIGNIFICANCE OF IMMUNOLOGICAL INVESTIGATIONS DURING RADIOTHERAPY FOR BREAST CANCER.

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Wien Klin Wochenschr; 93(17):547-551 1981

Immune response was measured in a group of 50 patients with carcinoma of the breast. Factors to be determined included (1) the influence of the tumor on immmunocompetence (IC), (2) the influence of removal of visible tumor on IC, (3) the influence of local irradiation on IC, (4) the influence of other therapeutic measures on IC, (5) indication of tumor recurrence or progression by IC parameters, and (6) indication of the course of disease by changes in IC during therapy. Parameters measured included IgA, IgG, IgM, IgE, lymphocyte migration, lymphocyte membrane fluorescence, T cell rosette formation, granulocyte phagocytosis, and reactions to skin tests. At the time of study 12 patients had died, 20 showed metastases, and 6 showed recurrence of tumor. Results were compared with results for patients with benign tumors and for healthy individuals. No useful clinical methods could be developed for early diagnosis, prognosis, or measurement of disease progress based on immune response. (23 Refs) (In GER)

47. ROLE OF ADHERENT SUPPRESSOR CELLS IN THE DEPRESSION OF CELL-MEDIATED IMMUNITY IN HODGKIN'S DISEASE AND LUNG CARCINOMA.

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Ann Immunol (Paris); 132(2):167-180 1981

The immunological status of 14 patients with Hodgkin's disease (HD) and 14 patients with lung carcinoma (LC) was studied to determine to what extent the depression of cell mediated immunity (CMI) analyzed by the lymphocyte reactivity to phytohemagglutinin (PHA) was caused by adherent suppressor cells and mediated by prostaglandins (PG) and to establish if such a mechanism could be involved in the depression of skin test reactivity in these patients. Of the 28 patients, 13 had depressed PHA response. In most of these cases, the depressed PHA response was mainly observed with suboptimal doses of this mitogen. In 3/9 HD cases and 2/4 LC cases, the suppression was caused by an excess production of PG by adherent cells. The role of PG as a mediator of this supression was indicated by the use of Ro 20-5720 which is an inhibitor of prostaglandin synthetase. By morphological criteria the adherent cells were monocytes. However , no clear-cut relationship could be established between the suppressive activity of adherent cells and the blood monocyte/lymphocyte ratio. No correlation was observed between depression of lymphocyte response to PHA and skin anergy. The results suggested that the depressed lymphocyte response to PHA of some cancer patients is attributable to adherent suppressor cells and to an excess of PG synthesis. (41 Refs)

48. LYSOZYME ENHANCES MONOCYTE-MEDIATED TUMORICIDAL ACTIVITY: A POTENTIAL AMPLIFYING MECHANISM OF TUMOR KILLING.

LeMarbre P, Rinehart JJ, Kay NE, Vesella R, Jacob HS
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Blood; 58(5):994-998 1981

The mononuclear phagocyte is well established as an in vitro cytotoxic effector cell for certain human tumors. The mechanism(s) for this action remains unclear. Increased levels of lysozyme, a cationic enzyme synthesized in large amounts by mononuclear phagocytes, are associated with increased resistance to transplantable animal tumors. In this study, we provide evidence that human lysozyme, isolated from the urine of leukemic patients, has marked potentiating effects on human monocyte-tumor-cell cytocidal activity. In addition, lysozyme-exposed monocytes incorporate increased quantities of leucine, suggesting that monocytes are capable of amplifying their own metabolic activation by secreting an endogenous constituent. Tri-N-acetyl-glucosamine, a competitive inhibitor for the active site of lysozyme, inhibits cytocidal activity. Conversely, protamine, an extraneous albeit similarly positively charged molecule, increases monocyte-mediated tumor cytotoxicity; this protamine effect is negated by heparin. We conclude that lysozyme, at least partially by its positive charge, is capable of enhancing in vitro monocyte tumor cell cytotoxicity; its in vivo secretion may potentiate monocyte-tumor-cell interaction. (Author abstract) (24 Refs)

49. IMMUNOLOGIC ASPECTS OF HEAD AND NECK CANCER.

Dichtel WJ
No affiliation given
Ear Nose Throat J; 60(10):486-492 1981

Components of the immune system and current methods of assessing the immune response are described; the relative immunoincompetence noted in patients with cancers of the head and neck is detailed. Because the cell-mediated or T-cell system has been shown to be the most vital component in the immune surveillance system, assays of T-cell-system activity may be important in the evaluation and care of patients with cancers of the head and neck. Such assays include skin testing, T-lymphocyte counts, in-vitro T-cell activity testing, and study of lymph-node morphology from resected specimens. Immunotherapeutic agents that have been used or investigated in head and neck cancers are discussed, including BCG, levamisole, thymosin, interferon, isotopically tagged antitumor antibodies, and transfer factor. (45 Refs)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

50. SUBPOPULATIONS OF SUPPRESSOR CELLS IN CHICKENS INFECTED WITH CELLS OF A TRANSPLANTABLE LYMPHOBLASTIC LEUKEMIA.

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Infect Immun; 34(2):526-534 1981

Three distinct subpopulations of cells with suppressor activity were separated by Ficoll density gradient centrifugation methods from the spleens of 3-to 4-wk-old chickens infected with cultured lymphoblastoid cells (JM-VLC), derived from JM-V leukemia: (i) a subpopulation of nonadherent cells, which separated in the T-cell-rich gradient fraction of leukemic chicken spleens, inhibited proliferative responses to concanavalin A in mixed cultures with normal chicken spleen cells; (ii) phagocytic cells (macrophages), which were the most effective suppressor cells of all subpopulations in the mixed culture assay, were recovered among the cells of greatest density in the spleens of both normal and leukemia chickens; (iii) JM-VLC cells in the buoyant gradient fractions of leukemia chicken spleens also effected suppression. In the later stages of lymphoproliferative disease, the number of spleen cells of buoyant density was increased, apparently as a result of infiltration of the spleens with JM-VLC cells. (Author abstract) (27 Refs)

51. INHIBITION OF ANTIGEN-INDUCED T-CELL PROLIFERATION BY ANTIBODIES TO ENDOGENOUS AKR-MULV.

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Cell Immunol; 64(1):102-118 1981

Lymph node cells from BALB/c mice immunized with ovalbumin or human gamma-globulin were restimulated in vitro with these antigens and assayed for antigen-induced proliferation. The proliferative response was shown to be antigen specific and T cell dependent. A rabbit antiserum to envelope and core proteins of AKR murine leukemia virus was found to inhibit antigen-induced T-cell proliferation. The IgG fraction and F(ab')2 fragments of the antiserum were also inhibitory. The inhibition occurred after the initial step of antigen-T cell interaction and viral absorption studies showed the inhibition to be specific for anti-AKR virus antibodies. A hypothesis for the mechanism of iahibition is discussed in relation to a functional role for endogenous murine leukemia virus. (Author abstract) (36 Refs)

52. LYMPHOPROLIFERATION AND HETEROTRANSPLANTATION IN NUDE MICE: TUMOR CELLS IN HODGKIN'S DISEASE.

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Haematol Blood Transfus; 26:229-234 1981

Histologically proven Hodgkin's disease (HD) derived material was used to establish four long term cultures. These in vitro cells had morphologic, cytochemical and cytogenetic features of their in vivo ancestors. Two of these cultures were obtained from pleural effusions of HD nodular sclerosing type, Stage IV B (diagnosed, one in 1972 and another in 1976). They shared these same features: non-B-T lymphocytes, non-macrophages, non myeloid cells, Epstein-Barr virus genome negative, monoclonality, multiple numerical and structural chromosome aberrations, and tumor formation after intracranial xenotransplantation in nude mice. After sc inoculation both lines failed to induce tumors. When one of them was embedded in a fibrin clot prior to transplantation, infiltrative tumor growth resulted after sc inoculation. Morphology of the two cell lines was very similar to Hodgkin (H) and Sternberg-Reed (SR) cells. Biological and immunological characterization of the two lines showed identical pattern observed in freshly prepared H and SR cells. They resemble very closely cultured H cells described by Kaplan. (14 Refs)

53. INCREASED NATURAL HOST RESISTANCE MECHANISMS IN B LYMPHOCYTE-DEPRIVED MICE.

Brodt P, Kongshavn P, Vargas F, Gordon J
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J Reticuloendothel Soc; 30(4):283-289 1981

The natural host resistance (NR) of mice injected with anti-IgM from birth was compared with that of normal rabbit globulin-treated animals in three systems: (a) hybrid resistance to tumor and bone marrow cells, and early T lymphocyte-independent elimination of (b) the intracellular parasite Listeria monocytogenes and (c) the extracellular parasite Trypanosoma musculi. Natural resistance was significantly increased over control in the three systems in vivo in parallel with an increase of natural killer cell activity previously established in vitro in these mice. Data are presented which suggest that NR measured in the different systems may be mediated by different effector cells. (Author abstract) (20 Refs)

54. VARIANTS FROM A MLV-INDUCED LYMPHOMA SELECTED FOR DECREASED SENSITIVITY TO NK LYSIS.

Gronberg A, Kiessling R, Eriksson E, Hansson M
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden
J Immunol; 127(5):1734-1739 1981

Variants with low sensitivity to natural killer- (NK) mediated lysis have been derived from the highly NK-sensitive YAC-1 lymphoma by in vitro selection with spleen cells from the NK high reactive (A x CBA) F1 hybrid, followed by passage of the surviving cells in vivo in the same F1 hybrid. Six independent variants were selected and all showed a marked reduction in sensitivity to lysis by mouse NK cells after 8 to 10 selection cycles. A general lower sensitivity was also seen when human PBL were used as effector cells. The NK-resistant variants were shown to be selectively resistant to lysis by NK cells because they displayed an equal or higher sensitivity to lysis by allospecific cytotoxic T lymphocytes than YAC-1. The basis for the resistance appeared to be a lower expression of the 'NK target structure' because the variants have a decreased ability to compete against YAC-1 in a cold target competition assay and to bind lymphocytes in a target-binding assay. A lower expression and not a complete lack of the target structure was also indicated by the fact that a great deal of the resistance could be overcome by using virus-activated NK cells. The selection procedure did not cause any decrease in serologically defined H-2 expression on the variants as compared to YAC-1. Their ability to adsorb the previously described 'NK-related' natural antibodies in rabbit serum was, however, decreased, which supported the notion that the antigen recognized by natural antibodies in normal serum may be related to the NK target structure. The use of variant cell lines, differing in NK sensitivity, may provide a valuable system for the biochemical characterization of the 'NK target structure' and the analysis of the in vivo role of NK cells. (Author abstract) (21 Refs)

55. INVOLVEMENT OF A RADIORESISTANT CELL IN THE PRODUCTION OF CIRCULATING INTERFERON INDUCED BY NOCARDIA FRACTIONS IN MICE.

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J Reticuloendothel Soc; 30(4):247-257 1981

Circulating interferon induction by the immunostimulant Nocardia fractions Nocardia water soluble mitogen (NWSM), Nocardia water soluble mitogen pellet (NWSMP) and peptidoglycan was studied in nude and irradiated mice. The three fractions were active in nude mice, suggesting that cells of thymic origin are not required for interferon synthesis induced by these fractions. NWSM and NWSMP were capable of interferon induction in irradiated mice, but peptidoglycan was inactive. Interferon titers induced by NWSM and NWSMP in irradiated mice were similar to those obtained in normal mice. these results indicate that the cell population (probably macrophages), involved in NWSM- and NWSMP-induced interferon production was radioresistant, whereas the presence of a radiosensitive cell population (probably lymphocytes) was necessary for interferon synthesis induced by peptidoglycan. The antigenic properties and pH stability of interferon induced by the different Nocardia fractions in nude and irradiated mice were examined. The interferon induced by peptidoglycan in nude mice appeared to be related to Type II (now called gamma) interferon. NWSMP, which induced a Type I interferon in normal and nude mice, had the same activity in irradiated mice. NW SM, which contains both NWSMP and peptidoglycan, induced Type I interferon in irradiated mice. NWSM and NWSMP were active interferon inducers in several mouse strains, including endotoxin-resistant C3H/HeJ mice. (Author abstract) (41 Refs)

56. PROLIFERATIVE AND CYTOTOXIC IMMUNE FUNCTIONS IN AGING MICE: I. SEQUENCE OF DECLINE OF REACTIVITIES MEASURED UNDER OPTIMAL AND SUBOPTIMAL SENSITIZATION CONDITIONS.

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Immunology; 44(3):607-616 1981

Individual young adult, middle-aged, and old C57BL/6J male mice were tested for in vitro generated proliferative and cytotoxic responses to H-2 alloantigens under a variety of sensitization conditions. Proliferation in mixed lymphocyte culture (MLC) had decreased by 14 mo of age (middle-aged), whether measured by directly assaying cultures in microtiter plates (micro MLC) or by labelling aliquots taken from large culture tubes (macro MLC). Cytotoxicity did not decline until a later age if sensitization was done in large tubes (macro cell-mediated lympholysis, CML). When cytotoxic activity was assayed by measuring lysis after addition of chromated cells to MLCs in microtiter plates (micro CML), differences were revealed between young and middle-aged animals. However, these conditions were suboptimal for generation of cytotoxicity even in young controls and showed even lower responses in the middle-aged group. It was concluded that proliferation showed an earlier, more severe decline than cytotoxicity with age as the proliferative response had declined by middle-age under all sensitization conditions used. With optimal sensitization conditions, senescent mice (26-30 mo) showed a 4-to 10-fold decrease in cytotoxicity compared with young adult mice. (Author abstract) (21 Refs)

57. NATURAL KILLER CELL ACTIVITY IN RETICULUM-CELL SARCOMAS OF SJL/J MICE. III. CHARACTERIZATION OF THE EFFECTOR CELLS WITHIN RCS THAT MEDIATE NK LYSIS.

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Dept. Microbiology-Immunology, Northwestern Univ. Medical Sch., Chicago, IL, 60611
Int J Cancer; 28(5):635-645 1981

Various cell depletion techniques were employed to identify the cells responsible for the natural killer (NK) activity against YAC-1 targets that is present in lymphoid tissues of SJL/J mice bearing transplantable reticulum-cell sarcomas (RCS). The NK-activating potential of irradiated RCS cells (X-RCS) allowed a comparison of three NK-cell activities in this model system: conventional, induced and RCS-cell-mediated cytotoxicity, represented by effector cells derived from lymphoid tissues of normal, X-RCS-injected and RCS-bearing donors, respectively. Both the conventional and induced NK cells were resistant to pretreatment with anti-Ia serum and C, whereas RCS-mediated NK activity was significantly red uced by similar antiserum treatment. The cytotoxicity expressed by both conventional and induced NK cells was moderately radiosensitive, however, 5-to 10-fold higher doses of irradiation were required to effect an equivalent reduction of RCS-mediated NK activity. To further characterize the effector cells that mediated RCS-associated Nk activity, viable RCS tumor cells were injected into SJL F1 hybrids that either supported (SJL x C57BL/6 and SJL x A.TH) or did not support [SJL x B10.S(7R)] RCS growth. After pretreatment of RCS cell preparations taken from these F1 mice with alloantisera directed against the non-SJL parental H-2 haplotype, to remove F1 host cells (F1 purified RCS), greater than 75% of NK activity was recovered in the RCS-injected SJL x C57BL/6 and SJL x A.TH F1 hybrids; however, less than 15% of NK activity was apparent in RCS-injected SJL x B10.S(7R) F1 recipients. 89Sr treatment of SJL mice abrogated their ability to show increased (induced) NK activity following injection of X-RCS. In contrast, viable F1-purified RCS cells demonstrated both growth and NK activity in 89Sr-treated SJL mice that was comparable to that seen in normal controls. Treatment of effector cells with three different NK-reactive antisera (alphaLy-11.2, alphaNK-1.2 and alphaasialo-GM1) effectively depleted conventional and induced NK activities, but had a minimal effect on RCS-cell-mediated NK cytotoxicity. These data support the conclusion that RCS tumor cells of SJL/J origin possess NK cytotoxic function and that, by virtue of their pre-B-cell characteristics, they may represent a unique class of NK effectors. (Author abstract) (34 Refs)

58. NATURAL KILLER CELL ACTIVITY IN RETICULUM-CELL SARCOMAS OF SJL/J MICE. II. ANALYSIS OF RCS-ASSOCIATED NK ACTIVITY.

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Dept. Microbiology-Immunology, Northwestern Univ. Medical Sch., Chicago, IL, 60611
Int J Cancer; 28(5):627-634 1981

Lymphoid cells taken from the grossly enlarged lymph nodes (LN) and spleens of SJL/J mice bearing transplantable reticulum-cell sarcomas (RCS), showed increased levels of natural killer (NK) cell activity, when compared to LN and spleen cells taken from normal SJL mice. The NK susceptible target cells used for these studies included RLmale-I and YAC-I. Target cells that were not susceptible to NK lysis by CBA/J effector cells (high NK strain) were also resistant to lysis by RCS tumor cells. Although significant lysis of target cells was detectable at 4 hr, optimal NK cytotoxicity was observed in a 16-hr 51Cr-release assay. In terms of lytic units (LU)/10(7) effector cells, greater NK activity was observed in RCS effectors than was apparent in normal CBA/J lymphoid cells. Depletion of macrophages from RCS cell preparations had no effect on the observed NK activity. Purified Mu-IFN-alpha stimulated a small increase in t he NK activity expressed by SJL lymphoid cells; however RCS-derived supernatants (containing Mu-IFN-gamma) did not augment NK activity of SJL effector cells, nor were they cytotoxic for NK target cells. Therefore, tumor-derived soluble factors appear not to be involved in the observed RCS-associated NK activity. The data presented in this report further define the parameters of the NK activity manifested by RCS tumor cell preparations. The accompanying article characterizes the nature of the NK effector cells present within RCS tumors of SJL mice. Taken together, these data indicate that the RCS tumors represent either neoplastic expansion of conventional NK cells with somewhat modified properties, or else an entirely new class of cytotoxic effector cells. (Author abstract) (31 Refs)

59. NATURAL KILLING (NK) AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC) IN SPECIFIC PATHOGEN-FREE (SPF) MINIATURE SWINE AND GERMFREE PIGLETS: III. TWO DISTINCT EFFECTOR CELLS FOR NK AND ADCC.

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J Immunol; 127(5):2190-2193 1981

Effect of 'anti-NK' sera on NK and ADCC activities was examined to study further the relationship between the effector cells for NK and ADCC in specific pathogen-free miniature swine. An appropriate dilution of 'anti-NK' sera that had no effect on ADCC activity not only inhibited NK activity but also eliminated NK cells in the presence of C which supports the presence of NK cells distinct from K cells for ADCC. (Author abstract) (20 Refs)

60. DEFINITIVE EVIDENCE THAT NATURAL KILLER (NK) CELLS INHIBIT EXPERIMENTAL TUMOR METASTASIS IN VIVO.

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J Immunol; 127(5):1754-1758 1981

Effector lymphoid cells that inhibit hematogenous tumor metastases in normal unimmunized mice were studied. Mice pretreated with cyclophosphamide (Cy) exhibited a diminished ability to destroy circulating tumor cells, which, in turn, caused an increased incidence of experimental pulmonary metastasis. Adoptive transfer of spleen cells from unimmunized syngeneic donors abrogated the Cy-induced enhancement of metastasis formation. The effector cell active in these adoptive transfer experiments was sensitive to treatment with specific anti-NK-1.2 antibodies and complement. This treatment was shown by in vitro tests to deplete or inactivate NK cells selectively. These findings provide direct evidence that NK cells play a significant role in the inhibition of hematogenous tumor metastasis in vivo. (Author abstract) (26 Refs)

61. SEPARATION AND CHARACTERIZATION OF THE NEOPLASTIC AND STROMAL ELEMENTS OF THE R323OAC MAMMARY ADENOCARCINOMA.

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Cancer Res; 41(12):5064-5069 1981

The purification of the various types of cells in solid tumors is necessary for study of their biochemical and immunological functions. The R3230AC adenocarcinoma contains both a variety of stromal cells and well-differentiated neoplastic cells that possess many of the biosynthetic capabilities of normal rat mammary cells. Suspensions of cells from tumors weighing less than 1.2 g consisted of 70.4 +-7.2% (SD) malignant cells by morphology, 6.8 +-3.0% lymphocytes, 6.3 +-3.2% macrophages, 15.2 +-5.2% RBC, 0.8 +-0.5% granulocytes, and 0.5 +-0.6% unidentified cells. Sedimentation of the cells from the R3230AC tumor in a previously described isokinetic gradient resulted in a 5-to 6-fold purification of lymphocytes and macrophages. The modal fraction of malignant cells contained 95.3 +-2.9% malignant cells. Detection of alpha-lactalbumin by the direct peroxidase conjugate technique gave vacuolar staining of malignant cells, in contrast to the indirect and peroxidase-antiperoxidase techniques which stained ducts from normal lactating mammary gland and a wide variety of cells without vacuoles in the tumor. The best fixative for frozen sections, paraffin-embedded tissue, and cell suspensions was 50% ethanol:50% acetone. The suspensions of tumor cells contained 14.4 +-9.4% cells with histochemically demonstrable alpha-lactalbumin. Squamous metaplasia was commonly observed in tumors from lactating rats. (Author abstract) (41 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

62. ENHANCEMENT OF CYTOTOXICITY OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES BY INTERFERON.

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Microbiol Immunol; 25(8):837-845 1981

The usefulness of the human lung carcinoma cell line (Pc-10) and Pc-10 cells persistently infected with mumps virus (Pc-10/MpV) as target cells for analyzing the relationship between alpha-interferon (IFN-alpha) and human natural killer (NK) activity was examined. Both Pc-10 and Pc-10/MpV were found to be useful as target cells. Pc-10/MpV were lysed more efficiently that uninfected Pc-10 cells by the same lymphocyte subpopulation, namely non-T, non-B cells, which correspond in part to NK cells. Human peripheral blood mononuclear leukocytes (PBML) were obtained from healthy donors who had antibody against mumps virus in their blood and were sensitive to mumps virus antigens in the skin reaction; no T cell-dependent cytotoxicity for Pc-10/MpV cells was observed. NK activity and the production of IFN/alpha in human PBML could not be dissociated, since anti-IFN-alpha suppressed the NK activity of PBML. Augmentation of the cytotoxicity of PBML by IFN-alpha was detectable within 2 hr of incubation. The effect of IFN-alpha on the augmentation of the cytotoxicity of human PBML for Pc-10 was dependent on the dose from 0.8-60 IU/ml. No difference between the augmentation of the cytotoxicity of human PBML by gamma-interferon and IFN/alpha was observed. (39 Refs)

63. POLYENZYMATIC ACTIVATION OF CELLULAR HYDROLASES INDUCED BY INTERFERON; ITS ROLE IN CELL LYSIS AND OTHER INTERFERON-RELATED PHENOMENA.

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Biomedicine; 34(4):82-88 1981

Treatment of human cultured T cells by interferon (IFN), which enhances cell-mediated cytotoxicity directed against human K562 cell targets (NK-like activity) induces on activation of cell hydrolases. Treatment of mouse cultured L929 cells by IFN and double strand RNA enhancing cell autolysis induces first an activation of tested hydrolases (hexosaminidase, beta-glucuronidase, acid phosphatase and alkaline phosphatase). Polyenzymatic activation of hydrolases induced by IFN is similar to coordinate enzymatic induction described by Hosli which occurs by lack of specific enzyme when non-digestible substrates are absorbed by cells. It is hypothesized that the polyenzymatic activation which accounts for cell lysis is a general defense mechanism which might also explain other actions related to IFN such as antiviral effect, inhibition of cell division, diminution of protein synthesis and cell surface alteration. (Author abstract) (23 Refs)

64. EFFECT OF BETA ADRENERGIC AGONISTS AND BETA BLOCKING AGENTS ON HEMOPOIESIS IN HUMAN BONE MARROW.

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Biomedicine; 34(4):93-98 1981

The effect of propanolol (nonspecific blocking agent), acebutol (beta1 blocking agent), butoxamine (beta2 blocking agent) and several beta adrenergic agonists was studied on 3H-thymidine (3H-TdR) incorporation and granulomonocyte colony formation in agar by human bone marrow. Only butoxamine and propanolol decreased 3H-TdR incorporation by total normal bone marrow cells at concentrations above 10(-6) M for butoxamine and 10(-5) M for propanolol. Autoradiography showed that inhibition of 3H-TdR incorporation by butoxamine was slightly more pronounced on neutrophil precursors than on red cell precursors (neutrophil series LI..53 and erythroblasts .67 compared to control bone marrow cells at 10(-5) M concentration). The development of granulo-monocyte colonies in agar culture was delayed by preincubation with butoxamine at concentrations above 5 x 10(-6) M. Hydroxyurea suicide showed that this was due to a decrease in the number of CFU-C in S phase. Beta2 blocking agents are able to decrease the number of normal hematopoietic cells entering S phase. This effect is seen on both neutrophil and erythroblastic precursors and on granulo-monocyte progenitors. It could be used as a means of protecting bone marrow cells during cancer intensive chemotherapy. (Author abstract) (18 Refs)

65. THE INDUCTION OF AT LEAST TWO DISTINCT TYPES OF INTERFERON IN MOUSE SPLEEN CELL CULTURES BY CORYNEBACTERIUM PARVUM.

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Cell Immunol; 64(1):64-72 1981

Stimulation of dissociated C57Bl/6 mouse spleen cells with Corynebacterium parvum resulted in the production of interferon (IFN) activity that was only partially neutralized by separate treatment with anti-L-cell IFN (anti-IFN-alpha/beta) or anti-gamma IFN (anti-IFN-gamma) antisera. Treatment of the IFN preparation simultaneously with the two antisera resulted in complete neutralization of antiviral activity, thus C parvum induced both IFN-alpha/beta and IFN-gamma in spleen cells. The total number of units of antiviral activity in untreated cultures was greater than the sum of the titers of the individual IFNs. This is consistent with the phenomenon of 'potentiation', where mixtures of IFN-alpha/beta and IFN-gamma have been shown to exhibit increased antiviral activity. Kinetic studies showed that IFN-alpha/beta activity in cultures peaked at 12 to 24 hr, while IFN-gamma peaked at 48 to 72 hr. The different IFNs induced by C parvum were separated by gel filtration chromatography, with IFN-alpha/beta exhibiting a mol wt of about 25,000 daltons and IFN-gamma a mol wt of 35,000 to 40,000 daltons. Separation of the spleen cells into plastic-adherent and nonadherent populations showed that nonadherent cells were the major producers of both IFN-alpha/beta and IFN-gamma following stimulation with C parvum. Treatment of spleen cell cultures with monoclonal anti-Thy 1.2 antibody and complement greatly reduced the production of IFN-gamma but had little or no effect on the production of IFN-alpha/beta. These data suggest that T lymphocytes are the producers of IFN-gamma, and that IFN-alpha/beta is produced by a nonadherent, non-T cell. Preliminary data suggest that the IFNs may play a role in C parvum-induced immunosuppression. (Author abstract) (20 Refs)

66. LYMPHOKINE PRODUCTION BY PERIPHERAL BLOOD LEUCOCYTES: QUANTITATION OF T-CELL GROWTH FACTOR ACTIVITY FOR ASSESSMENT OF IMMUNE RESPONSE CAPABILITY.

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Aust NZ J Med; 11(5):475-479 1981

Mitogen stimulation of as few of 200,000 human peripheral blood leukocytes (PBL) in 0.2 ml vol produces highly active lymphokine supernatants. The lymphokine activity measured is T-cell growth factor. Under optimum conditions of PHA-P concentration, serum source and concentration, and time, activity is detectable to a dilution of between 1/250 and 1/700 for lymphokine supernatants from PBL of normal donors. Lymphokine supernatants prepared from PBL of donors previously treated with the immunosuppressive regimes of radiotherapy and/or chemotherapy had activities that were between 13% and 66% of normal controls. Lymphokine production as a quantitative measure of immune capability is discussed. (Author abstract) (11 Refs)

67. INFECTIONS AND NATURAL KILLER CELL.

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Nippon Rinsho; 39(6):50-52 1981

Natural killer cell damage of virus-infected cells and current questions concerning cell-mediated natural resistance to infection were discussed. Focusing on natural killer cell damage of virus-infected cells, the role of interferon in the process of controlling proliferation of cancer cells was reviewed. With respect to cell-mediated resistance, 89Sr has been shown to damage hybrid resistance, natural killer cell activity, early stage defense against Listeria infection, defense against Friend virus-induced leukemia, and early stage defense against Herpes simplex Type I virus, but the form that this damage of marrow cells takes has yet to be clarified. (2 Refs) (In JPN)

68. IS BROMOCRIPTINE (CB-154) AN ANTIMITOTIC DRUG? EXPERIMENTAL EVIDENCE.

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Patologia Medica IIR, Univ. Pisa, Pisa, Italy
Drugs Exp Clin Res; 7(5):649-652 1981

The effects of increasing doses of Bromocriptine (CB-154) on cells with high DNA synthesis activity was investigated. Samples of heparinized peripheral venous blood (20 ml) from 15 healthy donors were employe according to a previously reported method with minor modifications. The mitotic activity was evaluated by the addition of methyl 3H thymidine 3H TdR to the culture and subsequent measurement in a scintillation counter. CB-154 was found to reduce the response of lymphocytes not treated with phytohemagglutinin (PHA) by 92.8%, 71.9%, and 28.2% for doses of 20, 5, and 1 ug respectively. Response of cells stimulated with PHA was reduced 83.1%, 58.5%, and 9.9% with doses of 20, 5, and 1 ug respectively. Viability was reduced 50% using 20 ug CB-154 with or without PHA. Results suggest that CB-154 has an inhibitory action on DNA synthesis in cultured lymphocytes. Apparently, the highest doses have a cytotoxic mechanism; consistent decreases in lymphocyte viability occurred only with 20 ug of the drug. Minor doses impaired thymidine incorporation. This effect is more pronounced in cells treated with PHA, apparently indicating a partially reversible process. (13 Refs)

69. IMMUNOPOTENTIATION OF TUMOR-BEARING AND TOXOHORMONE-TREATED MICE BY HUMAN CERULO PLASMIN.

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Gan; 72(5):673-678 1981

Human ceruloplasmin was shown to have a restorative effect on the decrease of delayed hypersensitivity in sarcoma-180-bearing mice and of helper T-cell activity in cell-free Ehrlich cancerous ascitic fluid-treated mice. Furthermore, it was also shown that ceruloplasmin augments the in vivo generation of alloreactive cytotoxic cells which consist of cytotoxic T-lymphocytes, cytotoxic macrophages and K cells. (Author abstract) (36 Refs)

70. ELIMINATION OF TUMOR-ENHANCING CELLS BY CYCLOPHOSPHAMIDE AND ITS RELEVANCE TO CYCLOPHOSPHAMIDE THERAPY OF A MURINE MAMMARY TUMOR.

Nakajima H, Abe S, Masuko Y, Tsubouchi J, Yamazaki M, Mizuno D
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Gan; 72(5):723-731 1981

The antitumor effect of cyclophosphamide (CY) on a syngeneic mouse mammary tumor, MM46, was found to be due to selective elimination of host lymphoid cell populations as well as a direct cytotoxic effect of CY on tumor cells. Marked inhibition of tumor growth after a single ip injection of CY on day 12 lasted for more than 3 wk, unless the host was infused iv with spleen cells from tumor-bearing mice. The tumor-enhancing activity of spleen cells from tumor-bearing mice appeared to be mainly due to Thy 1.2 positive T lymphocytes and was no longer seen after CY treatment on day 12. The extent of tumor growth inhibition achieved with CY was critically dependent on the time of drug administration. CY had no antitumor effect when given before tumor inoculation. Associated with the antitumor effect of CY, augmentation of the antitumor delayed hypersensitivity reaction, or the cellular immune response, was observed. In contrast, the titer of antitumor antibody in the blood, or the humoral immune response, decreased. Cell transfer experiments showed that suppressor T cells for antitumor delayed hypersensitivity reaction specifically induced by the tumor inoculum were eliminated after CY treatment on day 12. (Author abstract) (39 Refs)

71. THE MECHANISM OF SPECIFIC SUPPRESSION IN EFFECTOR T CELL CLONES AGAINST TUMOR-ASSOCIATED TRANSPLANTATION ANTIGENS.

Fujiwara H, Tsuchida T, Mizuochi T, Kohmo T, Hamaoka T
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Gan; 72(5):732-741 1981

The present study investigates the fate of effector T cell population against tumor-associated transplantation antigens (TATA) of X5563 plasmacytoma in syngeneic mice rendered specifically unresponsive to the TATA. In this tumor system, T cell-mediated tumor-specific immunity was induced by id inoculation of viable tumor cells followed by the surgical resection of the tumor (immunization procedure). The iv presensitization of syngeneic hosts with X-irradiated tumor cells abolished the capability of those hosts to develop the tumor-specific immunity after the above appropriate immunization procedure. Spleen cells from the pretreated mice which subsequently received the immunization procedure could not regain the tumor-neutralizing activity after enzymatic treatment with papain. Moreover, lymphoid cells from the pretreated mice could not be stimulated by the immunization procedure even after proteolytic treatment with papain or trypsin, followed by transfer into other recipient mice free of the serum suppressive factor(s). On the other hand, such enzyme treatment was capable of preventing the tolerance induction of dinitrophenyl (DNP)-primed B cells after in vitro pulsing with DNP-D-GL (copolymer of D-glutamic acid and D-lysine) for 2 hr, suggesting that the enzymatic treatment used here was adequate to remove the blocked receptor and any tolerogen. These results suggest that in X5563 plasmacytoma system, the above specific unresponsiveness induced by the iv presensitization with TATA is due to the irreversible inhibition or deletion of effector T cell clones rather than mere effector cell blockade. (Author abstract) (24 Refs)

72. EFFECTS OF SURGICAL STRESS ON NATURAL KILLER ACTIVITY, PROLIFERATIVE RESPONSE OF SPLEEN CELLS AND CYTOSTATIC ACTIVITY OF LUNG MACROPHAGES IN RATS.

Toge T, Hirai T, Takiyama W, Hattori T
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Gan; 72(5):790-794 1981

The effects of surgical procedures such as thoracotomy and/or laparotomy on natural killer (NK) activity, proliferative response to phytohemagglutinin (PHA) of spleen cells and cytostatic activity of lung macrophages were investigated in rats. NK activities of rats that had undergone the surgical procedures were significantly depressed on Day 1. By Day 7, NK activity in the thoracotomy group exceeded that of normal rats, while the activity in the laparotomy group was similar to that in normal rats. However, NK activity in the laparothoracotomy group remained depressed. Spleen cell proliferative response to PHA was also significantly depressed on Day 1 in all groups, and in the laparothoracotomy group, a depressed response was still apparent on Day 14. The cytostatic activities of lung macrophages were significantly reduced in thoracotomy groups, but the effect was rather slight in the laparotomy group. It is likely that the extensive surgical stress of laparothoracotomy can depress the host's immunological reactivity and furthermore result in an enhancement of tumor growth. (Author abstract) (20 Refs)

73. MODULATION OF THE IMMUNE RESPONSE BY CHEMOTHERAPY.

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Section Medical Oncology, Dept. Medicine, Dept. Immunology, Rush-Presbyterian-St. Luke's Medical Center, 1753 W. Congress Parkway, Chicago, IL, 60612
Pharmacol Ther; 14(1):89-122 1981

The effects of drugs on immune response are reviewed. Immune response may be impaired or augmented by various drug treatments. Factors relevant to drug-induced immunosuppression include pharmacological action and pharmacokinetics of the drug, dosage and schedule of administration, the nature of the immune response investigated, and the influence of antigen administration schedule. Drugs may affect afferent immune responses, including the numbers and immunocompetence of monocytes, macrophages, and lymphocytes. Drugs may affect the central, or productive phase of immune response, including DNA synthesis and the differentiation of suppressor and effector cells. Effects on the efferent portion of immune response include changes in mature T cells and non-T cell-non-B cell effector functions. The effects of drugs may be affected by the condition of immune response prior to drug administration. Consideration of all these effects should facilitate design of therapies. (268 Refs)

74. HERPESVIRUS ATELES AND HERPESVIRUS SAIMIRI TRANSFORM MARMOSET T CELLS INTO CONTINUOUSLY PROLIFERATING CELL LINES THAT CAN MEDIATE NATURAL KILLER CELL-LIKE CYTOTOXICITY.

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Proc Natl Acad Sci USA; 78(10):6391-6395 1981

Herpesvirus ateles (HVA) and herpesvirus saimiri (HVS) have the capacity to transform cotton-topped marmoset T lymphocytes into continuously proliferating cell lines that retain some functions associated with cell-mediated immunity. In the present paper, we demonstrate that HVA/HVS-transformed T cell lines are cytotoxic in a short-term 51Cr release assay and that this killing resembles killing by marmoset natural killer (NK) cells. The relationship between NK cells and HVA/HVS-transformed killer cell lines is discussed in view of present knowledge of the origin and function of the NK system. It is suggested that the described cytotoxic cell lines may be useful for further defining cellular cytotoxicity with regard to cell surface recognition, regulatory events, and lytic mechanisms. (Author abstract) (37 Refs)

75. INTERFERENCE OF GLUCOSAMINE AND OTHER AMINOSUGARS ON BLAST TRANSFORMATION.

Mazzuca A, Maldini M, Andollina A
Laboratorio Analisi Cliniche, Ospedale M. Malpighi, Bologna, Italy
Boll Soc Ital Biol Sper; 57(11):1274-1277 1981

The toxicity of glucosamine and other aminosugars on normal and neoplastic cells was studied in mitogen-induced lymphocytes. Incorporation of labeled leucine, uridine, and thymidine, precursors of protein, RNA and DNA, respectively, was strongly inhibited in blast cells exposed in vitro to D-glucosamine, D-galactosamine, and D-mannosamine. The possibility that glucosamine interfers with protein synthesis by preventing glucose metabolism was examined by adding increasing units of glucose or pyruvate to the culture medium. The results indicated that added glucose and pyruvate did not decrease the inhibitory effect of glucosamine. Glucosamine-6P, acetylglucosamine, and acetylgalactosamine produced only 20% inhibition when used at the same molar concentrations as glucosamine, galactosamine, and mannosamine. Since glucosamine-6P produced relatively minor metabolic interference in comparison with that of glucosamine, it was suggested that glucosamine acts by interfering with the process of phosphorylation at various levels. It was suggested that the relative insensitivity of transforming lymphocytes to N-acetylglucosamine and N-acetylgalactosamine is based on their limited intracellular accumulation. (10 Refs)

76. THYMIN AND CELL MEDIATED IMMUNITY.

Jin Y
Dept. Biology, Nanjing Univ., Nanjing, People's Republic of China
Shengli Kexue Jinzhan; 12(2):126-131 1981

Research on the physiological role of thymus hormones in cell-mediated immunity is reviewed. The hormones act on immature lymphocytes of the thymus and peripheral blood to transform them into the mature T-lymphocytes that take part in cell-mediated immunity of the organism. They consist of a group of polypeptides and proteins; more than 20 have been isolated and named, including thymosin, thymopoietin I, thymopoitin II, thymin, and serum thymic factor. They have been used in China as immunologic regulators combined with chemotherapy in treating immunologic deficiency syndromes, autoimmune disease, and small cell carcinoma of the lung. Results so far have been very promising. The analysis of thymus hormones, the roles of cyclic nucleotides (cAMP and cGMP), and the role of aging in relation to the immune system are described. (48 Refs) (In CHI)

77. THE CONCEPT OF GVHD-SUPPRESSION BY IN VITRO TREATMENT WITH ANTISERA.

Rodt H, Thierfelder S, Kolb HJ, Netzel B, Haas RJ, Wilms K, Bender-Gotze C
Abteilung Immunologie, Institut fur Hamatologie, Landwehrstrasse 61, 8000 Munich 2, W. Germany
Haematol Blood Transfus; 26:124-135 1981

Data on the prevention of graft-versus-host disease (GvHD) by anti-T-cell globulin (ATCG) are summarized. Investigations are reported on the in vivo elimination mechanism of T cells which were pretreated with ATCG in vitro. The survey also includes approaches to suppress GvHD by monoclonal antibodies as well as investigations on the chimerism, immunocompetence, and tolerance in the transplanted animals. Complete recovery of immune functions after transfer of ATCG-treated marrow are described in chimeras in which hemopoietic stem cells and host thymus differed by both histocompatibility-2 haplotypes, including immune region-associated specificities. The first results of an application of bone marrow incubation in the clinical situation are described in which the marrow of 14 leukemic patients was preincubated with ATCG to prevent GvHD. Five patients had acute lymphoblastic leukemia (ALL), six had acute myelogenous leukemia, and three had T-cell ALL. In general engulfment and recovery of bone marrow functions after incubation treatment did not differ from that of earlier transplantations without ATCG. Of 14 patients, 12 showed an engraftment between days 13-26 after transplantation. Of the 12 patients, 7 were sex mismatched, and 3 showed ABO blood group incompatibility. In one patient each, sex and blood group or human leukocyte antigen D and blood group were different. Two patients did not show substantial engraftment. (23 Refs)

78. CORTICOSTEROID DEPENDENCE OF CONTINUOUS HEMOPOIESIS IN VITRO WITH MURINE OR HUMAN BONE MARROW.

Greenberg HM, Parker LM, Newburger PE, Said J, Cohen GI, Greenberger JS
(c/o Greenberger) Dept. Radiation Therapy, Harvard Medical Sch., 44 Binney St., Boston, MA, 02115
Haematol Blood Transfus; 26:289-293 1981

A system for continuous in vitro hemopoiesis using human marrow is reported Human marrow was obtained from biopsies of femur or rib. Cultures were grown under varying conditions. Production of granulocyte-macrophage progenitor cells (GM-CFUc) required freshly added hydrocortisone, as in murine marrow cultures. Further requirements, not necessary for murine marrow cultures, included delayed removal of RBC and pH 7.0-7.5 with PCO2 at 3-5%. Adherent cell populations showed more fibroblastic proliferation than murine cultures. Within fibroblasts and macrophages in the stroma were 'cobblestone' areas of tightly packed cells. Continuous human marrow cultures produced granulocytes with normal morphology which produced esterase and myeloperoxidase. Over 80% of cultures tested contained granulocytes and macrophages. Granulocytes showed normal ingestion, respiratory burst activity, degranulation, and bacterial killing. GM-CFUc were produced for more than 20 wk by the method. (16 Refs)

79. CHARACTERIZATION OF HEMATOPOIETIC TARGET CELLS OF DEFECTIVE AVIAN LEUKEMIA VIRUSES BY VELOCITY SEDIMENTATION AND DENSITY GRADIENT CENTRIFUGATION ANALYSES.

Graf T, Royer-Pokora B, Korzeniewska E, Grieser S, Beug H
Institut fur Virusforschung, Im Neuenheimer Feld 280, 6900 Heidelberg 1, W. Germany
Haematol Blood Transfus; 26:417-423 1981

The hematopoietic target cells of replication-defective viruses (DLV) were characterized according to physical parameters: sedimentation velocity at unit gravity (as a measure of relative size) and centrifugation in Percoll density gradients (to determine relative buoyant density). Included is a comparison of the DLV target cells to the normal granulocyte/macrophage colony-forming cells (CFU-C) which develop together with the DLV-transformed cells under the specified culture conditions. Results are discussed in relation to three categories according to the phenotype of differentiation expressed: AEV-type viruses - erythroblasts; MC29-viruses - macrophages; and AMV type strains - myeloblast-like transformed cells. Results show that in general target cells for all three DLV types were most abundant in fractions consisting mainly of blast-like, immature bone marrow cells. The target cells are similar to each other with respect to size and density. In comparison to RBC, granulocytes, and CFU-C cells they are relatively large; they are much lighter than RBC and granulocytes. Together with earlier results, results suggest that DLV target cells are immature but already committed to the erythroid or myeloid lineages and upon transformation DLVs block differentiation of their target cells. Data concerning the relationship between normal macrophage/granulocyte colony forming cells and the target cells of MC29 and AMC are incomplete but suggest they are not identical. (14 Refs)

80. REGULATION OF HUMAN T-CELL PROLIFERATION: T-CELL GROWTH FACTOR AND ISOLATION OF A NEW CLASS OF TYPE-C RETROVIRUSES FROM HUMAN T-CELLS.

Gallo RC, Poiesz BJ, Ruscetti FW
NCI, Bethesda, MD, 20014
Haematol Blood Transfus; 26:502-514 1981

Recent results with human T-cell growth factor (TCGF), the various T cell systems, and the isolation of a new type-C retrovirus released from growing T-cells from some of these T-cell neoplasias are summarized. Unlike normal T-cells, neoplastic mature T-cells respond directly to TCGF without prior lectin or antigen in vitro activation. Transformed T-cell lines exhibit phenotypic characteristics consistent with the neoplastic cells of their disease of origin. A new retrovirus, human T-cell lymphoma-leukemia virus (HTLV) was isolated from fresh and cultured cells from two patients, each with a variant of a cutaneous T-cell lymphoma. Further studies showed that HTLV was not significantly related to any known animal retrovirus, is not an endogenous (genetically transmitted) virus of man, and at present is only associated with fresh or cultured T-cells from patients with the T-cell neoplasia. The results suggest that HTLV infected some mature T-cells of some people and may be involved in some neoplasias involving these cells. (33 Refs)

81. LYMPHOKINE PRODUCTION BY PHA-STIMULATED HUMAN LYMPHOCYTES IS ENHANCED BY INTERFERON.

Blomgren H, Einhorn S
Radiumhemmet, Karolinska Hosp., Post Office Box 60500, S-104 01 Stockholm, Sweden
Int Arch Allergy Appl Immunol; 66(2):173-178 1981

Human interferon (IFN) was examined for its capacity to modify the phytohemagglutinin (PHA)-triggered release of mitogenic factors (MF) from human lymphocytes in vitro. It was observed that the presence of partially purified leukocyte IFN (IFN-alpha) during the PHA pulsing of the lymphocytes increased their subsequent release of factors which were mitogenic for fractionated T cells. A similar effect was also observed when lymphocytes were exposed to IFN-alpha prior to PHA pulsing. The possibility that substances in the IFN preparations other than IFN are responsible for the above effect is ruled out by the finding that a pure fibroblast IFN (IFN-beta) preparation also augmented the MF release by PHA-pulsed lymphocytes. (Author abstract) (22 Refs)

82. REGULATION OF HUMAN NATURAL KILLING. I. THE ROLE OF MONOCYTES, INTERFERON, AND PROSTAGLANDINS.

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J Immunol; 127(5):2007-2013 1981

We have found that human endogenous natural killer activity as measured in a rapid 51Cr release assay is unaffected by the presence of monocytes. Moreover, stimulation of natural killer cells by poly I:C is independent of monocytes. In contrast, the presence of monocytes in a mixed population of mononuclear cells that have been stimulated by poly I:C suppresses NK activity. The suppression is shown to be partially reversible if indomethacin (10(-6) M) is added to the cultures during stimulation. Culture supernatants of monocytes stimulated with poly I:C are shown to contain PGE1 in a radioimmunoassay, and have NK inhibitory activity comparable to that obtained with exogenous PGE1 added to NK assays at a concentration range of 10(-7) to 10(-9) M. Culture supernatants from poly I:C-stimulated monocytes do not have detectable levels of antiviral activity. In contrast, plastic nonadherent cells stimulated with poly I:C produce significant levels of interferon (100 to 200 U/ml/2 x 10(6) cells) but almost undetectable amounts of PGE. Supernatants of nonadherent cells incubated with indomethacin (10(-6) M) alone augment NK activity. Taken together, the results suggest that stimulation of mononuclear cells with poly I:C is dependent on and regulated by the relative levels of interferon produced by lymphocytes and PGE produced by monocytes. (Author abstract) (52 Refs)

83. STIMULATION WITH AUTOLOGOUS LYMPHOBLASTOID CELL LINES: LYSIS OF EPSTEIN-BARR VIRUS-POSITIVE AND -NEGATIVE CELL LINES BY TWO PHENOTYPICALLY DISTINGUISHABLE EFFECTOR CELL POPULATIONS.

Zarling JM, Dierckins MS, Sevenich EA, Clouse KA
Immunobiology Res. Center, Univ. Minnesota, Minneapolis, MN, 55455
J Immunol; 127(5):2118-2123 1981

Human lymphocytes, stimulated in vitro for 6 days with x-irradiated or glutaraldehyde-treated autologous Epstein-Barr

(EB) virus-transformed lymphoblastoid cell lines (LCL), are cytotoxic for autologous and allogeneic EB+ LCLs as well as for several EB- cell lines that are also susceptible to lysis by interferon-activated natural killer (NK) cells. To determine whether the apparent nonspecific lysis mediated by LCL-stimulated cells is due to a mixture of effector cells directed against different target cells, advantage was taken of our recent finding that monoclonal antibody OKT8 reacts with human cytotoxic T lymphocytes but not with NK cells or NK-like cells generated in mixed WBC cultures. The depletion of OKT8+ cells from LCL-stimulated cultures by treatment with OKT8 and complement abolished or markedly depleted cytotoxicity against all EB+ target cells tested, whereas cytotoxicity against EB-, NK-sensitive cell lines including K562, MOLT-4 and HSB-2 was not or only minimally reduced. These results indicate that stimulation with autologous LCL results in the generation of OKT8+ cytotoxic T lymphocytes that lyse EB virus-transformed LCL and OKT8-NK-like cells that lyse EB-, NK-sensitive cells. (Author abstract) (36 Refs)

84. INTERFERON ACTS DIRECTLY ON HUMAN B LYMPHOCYTES TO MODULATE IMMUNOGLOBULIN SYNTHESIS.

Harfast B, Huddlestone JR, Casali P, Merigan TC, Oldstone MB
(c/o Oldstone) Dept. Immunopathology, Scripps Clinic and Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037
J Immunol; 127(5):2146-2150 1981

At different times of exposure, interferon (IFN) enhanced and suppressed pokeweed mitogen- (PWM) induced IgG synthesis by human peripheral blood lymphocytes (PBL). Pretreatment of PBL with IFN frequently increased antibody production by more than 100% when compared with that by untreated PBL. Results of experiments in which PBL were separated into T and B subpopulations indicated that IFN preparations acted directly on B cells. Thus, mixtures of IFN-treated B cells and untreated T cells from five of seven persons tested produced 81% to 500% more IgG than untreated, matched control cells. However, IFN-treated monocytes mixed with untreated B and T cells or IFN-treated T cells mixed with untreated B cells failed to enhance IgG production significantly in similar assays. In contrast to the pretreatment protocol, when IFN was present in the incubation mixture throughout the PWM assay, IgG production decreased. Sephadex chromatography of the IFN and tests of the resulting fractions indicated that the IgG production-enhancing activity was located in the fraction carrying the antiviral activity. (Author abstract) (33 Refs)

85. INDUCTION OF TARGET ANTIGENS AND CONVERSION TO SUSCEPTIBLE PHENOTYPE OF NK-CELL-RESISTANT LYMPHOID CELL LINE.

Clark EA, Sturge JC, Falk LA
Regional Primate Res. Center, Univ. Washington, Seattle, WA, 98195
Int J Cancer; 28(5):647-654 1981

Two autologous Herpesvirus papio producer lymphoid cell lines and one autologous non-producer line were compared for susceptibility to natural killer (NK) cell-mediated lysis. The non-producer cell line, 26CB-1, was more resistant to NK cell killing compared to one viral producer counterpart 13CB-I, but equally resistant when compared to another, 8CB-I. Treatment with chemical agents that affect differentiation or activate the viral cycle, including n-butyrate, IuDR, 5-azacytidine and tunicamycin, increased the susceptibility to killing of the non-producer line but had less effect on the 13CB-I producer line. The increase in susceptibility was due to induction of new target antigens: activated 26CB-I cells were more effective at inhibiting NK-cell-mediated lysis and were bound by more NK cells than untreated control cells. The expression of NK target structures may be related to the differentiated state rather than to the viral production status of target cells. (Author abstract) (43 Refs)

86. ENHANCING EFFECT OF INTERFERON (IF) ON THE INDUCTION OF KILLER T CELLS AGAINST ASCITES HEPATOMA (MH134) (MEETING ABSTRACT).

Unoura M, Hatano M, Kato Y, Kobayashi K, Hattori N
Dept. Virology, Cancer Res. Inst. Kanazawa Univ., Kanazawa-shi, Ishikawa Pref. 921, Japan
Proceedings of the 17th Annual Meeting of Japan Society of Hepatology held in Gifu, Japan, 25-26 June, 1981. Japan Society of Hepatology, Tokyo 113, Japan, 148 pp., 1981.

As in vivo treatment, female C3H/He mice, 8-to 12-wk-old at the beginning of the experiment, were left untreated (Group I), or given 2 x 10(4) unit of IF ip (Group II), 1 x 10(6) mitomycin C (MMC)-treated MH134 cells (derived from C3H/He mice) ip (Group III) or 2 x 10(4) unit of IF + 1 x 10(6) MMC-treated MH134 cells (Group IV). After 10 days of these treatments, the spleen cells of the mice were cultured alone (a), with MMC-treated MH134 cells (b), or with IF + MMC-treated MH134 cells (c) in vitro for 5 days. For the MMC treatment, 1 x 10(6) MH134 cells were treated with 100 ug of MMC for 45 min, and for the IF treatment, 1 x 10(6) MH134 cells were treated with 2 x 10(4) unit of IF for 2 hr. The cytotoxicity determined by 51Cr-release assay (effector, mouse spleen cells; target cells, MH134; effector/target ratio 40/1) during a 16-hr period after 5 days of in vitro culture which was begun 10 days after in vivo treatment for (a), (b) and (c), respectively, was 0%, 0% and 8.0%, in Group I; 13.6%, 22.8% and 19.3%, in Group II; 20.2%, 29.0% and 28.9% in Group III; and 48.4%, 40.3% and 56.7% in Group IV. When the spleen cells of the mice treated in the same way as c in Group IV were treated with anti-theta-antibody (theta) and complement (C), the cytotoxicity was 0% while it was 39.6% without the theta or C treatment and 34.9% with the C treatment alone. From the results of (a) in Groups I and II, IF was thought to augment the nonspecific cytotoxicity, and from those of (b) and (c) in Groups I and II, the recognizing potential of syngeneic tumors was thought to be augmented in the spleen cells of the mice given IF, and the tumors treated with IF to be more easily recognized. The results of (a) in Groups I, III and IV showed that when only a primary stimulus is given in vivo or when the secondary stimulus is given in vitro, the IF + MMC-treated MH134 tumor is most easily recognized. The effector in (c) in Group IV was shown to be the T cells. (no Refs) (In JPN)

87. SUPPRESSION OF LYMPHOCYTE PROLIFERATION BY HUMAN TUMOR CELLS GROWN IN SHORT TERM CULTURES.

Lafferty WE, Kempf RA, Goodwin JS
(c/o Goodwin) Dept. Medicine, Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131
J Clin Lab Immunol; 6(2):157-163 1981

The effect of short-term cultures of human tumor cells (less than 10 passages) added to mitogen- and alloantigen-stimulated cultures of peripheral blood monocyte cells (PBMC) on the proliferative responses of PBMC from natural donors was studied. At 1/10 and 1/100 tumor cell/PBMC ratios, only 1/7 tumor cell lines, (a melanoma) caused no suppression of phytohemagglutinin-stimulated cultures. Tumor cells were 50 x more suppressive than normal human fibroblasts. Similar results were obtained using concanavalin A. In mixed lymphocyte cultures, 1/10 tumor cell/lymphocyte ratios resulted in 66-85% suppression, while 1/100 tumor cell/lymphocyte ratios caused 43-66% suppression. Suppression of 3H thymidine incorporation of stimulated lymphocytes by tumor cell line T was evident throughout the 120 hr culture. PBMC recovery and viability were comparable after culture with and without tumor cell T. The percent suppression of 3H thymidine incorporation did not increase as the concentration of 3H thymidine decreased. Glass wool adherent cells were not required for suppression. The inclusion of the prostaglandin-inhibitor indomethacin had no effect on 3H thymidine incorporation by PBMC cultured with tumor cells. Mitomycin C completely abrogated the suppression by tumor T cells while irradiation with 1,000, 2,000, and 3,000 rad had little effect. Tumor cell line T inhibited 3H thymidine incorporation only when incubated in the same chamber with PBMC, not when separated from PBMC by a cell-impermeable membrane. Tumor cell line U, however caused 68% suppression when incubated in the same chamber with PBMC, and 46.4% inhibition across a cell-impermeable membrane. (27 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

88. ALPHA-1-ANTITRYPSIN IN HUMAN MACROPHAGES.

Isaacson P, Jones DB, Millward-Sadler GH, Judd MA, Payne S
Dept. Pathology, Level E, South Lab. and Pathology Block, General Hosp., Southampton SO9 4XY, England
J Clin Pathol; 34(9):982-990 1981

Preliminary studies have suggested that alpha-1-antitrypsin (A1AT) is a useful immunohistochemical marker of histiocytes (monocytes/macrophages) and malignant tumors derived from them. To confirm the reliability of this marker a wide variety of benign and malignant lymphoreticular cells and tissues have been stained by the immunoperoxidase technique for A1AT and positive staining was found to be confined to histocytes. Immunodiffusion, isotope labelling, and isoelectric focusing studies performed on cell lysates confirmed that the positive staining shown by monocytes and malignant histiocytes is due to the presence of A1AT identical with serum A1AT and that this material is synthesized by these cells rather than taken from their environment. Positive immunoperoxidase staining for A1AT is thus a reliable marker of lymphoreticular neoplasms of true histiocytic origin. (Author abstract) (19 Refs)

89. ACTIVATION AND MECHANISM OF ACTION OF SUPPRESSOR MACROPHAGES.

Lichtenstein A, Murahata R, Terpenning M, Cantrell J, Zighelboim J
Dept. Microbiology and Immunology, Univ. California Sch. Medicine, Los Angeles, CA, 90024
Cell Immunol; 64(1):150-161 1981

Iv administration of Corynebacterium parvum to alloimmunized mice activates splenic suppressor macrophages that effectively curtail primary and secondary generation of cytotoxic T lymphocytes (CTLs) in vitro. CTL generation was significantly inhibited in suppressed primary cultures by Day 3, the earliest time point that activity is first detected in control cultures. Suppressor macrophages had to be present during the first 24-48 hr of culture to effectively curtail the generation of CTLs. However, if suppressor macrophages were reactivated by 48-hr in vitro culture and then added to primary sensitizations that had been initiated 48 hr previously, they were capable of significant suppression. Suppressor cells produced a soluble factor that mediated the inhibition of CTL generation. The production or action of this factor could not be counteracted by indomethacin. (Author abstract) (31 Refs)

90. DIFFERENCES IN THE REGULATION OF MURINE GRANULOCYTE AND MACROPHAGE GROWTH IN DIFFUSION CHAMBER CULTURES (MEETING ABSTRACT).

Page PL, Robinson SH, Charles A
Department of Medicine, Beth Israel Hospital, Boston, MA, 02215
Exp Hematol; 9(Suppl9):159 1981

As demonstrated under four sets of experimental conditions, murine macrophages do not respond to the same factors which influence granulocyte proliferation in diffusion chamber (DC) cultures: (1) When normal mouse bone marrow cells are cultured in DCs, a plateau in cell growth is observed after 7-10 days. During this plateau phase the same number of macrophages is observed regardless of the number of marrow cells placed in culture, whereas the plateau number of granulocytes varies in relationship to the number of marrow cells in the culture inoculum. (2) When DC cultures are established with marrow cells from donor mice which have been pretreated with 3 doses of cytosine arabinoside during the 14 hr before culture, macrophage growth is similar to that observed with cultures of normal marrow cells. In contrast, granulocyte growth in cultures derived from the marrows of drug-treated mice is enhanced by a factor of two. (3) When DC cultures of normal mouse marrow are implanted in host mice which have received 500 R whole body irradiation 24 hr earlier, growth of macrophages is unchanged whereas granulocyte growth is augmented, as compared to the findings with control cultures grown in unirradiated host mice. (4) When normal mouse bone marrow cells and murine acute myelogenous leukemic cells are cocultured in DCs, macrophage growth is unaffected whereas normal granulocyte growth is entirely abolished within a few days. In all four of these experimental situations granulocyte proliferation, but not macrophage growth, correlated well with the generation of colony forming units (CFU-C), as examined by serially harvesting DC cultures and assaying the cell contents in soft agar with L-cell conditioned medium as a source of colony stimulating activity. (no Refs)

91. THE BINDING OF BCG-ACTIVATED MACROPHAGES TO TUMOR TARGETS STIMULATES SECRETION OF CYTOLYTIC FACTOR.

Johnson WJ, Whisnant CC, Adams DO
Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710
J Immunol; 127(5):1787-1792 1981

The binding of neoplastic targets and the secretion of a potent cytolytic protease (CF) by BCG-activated macrophages have previously been shown to be independent functions, both of which are necessary for completion of macrophage-mediated cytolysis. The present studies demonstrate that secretion of CF is triggered by the binding of neoplastic targets to BCG-activated macrophages. The binding of tumor targets, but not of normal lymphocytes, resulted in enhanced secretion of CF from BCG-activated macrophages, although not from macrophages elicited by thioglycolate broth. Dead or metabolically inactive tumor targets, as well as membrane preparations of tumor targets, induced secretion of CF from BCG-activated macrophages. The blocking of macrophage-target binding with a porous filter prevented augmented secretion of CF. Appreciable secretion of CF occurred in as little as 30 min after addition of tumor targets to BCG macrophages. Binding did not induce a generalized increase in secretion of neutral proteases by BCG macrophages, since secretion of plasminogen activator was actually decreased after the binding of P815 targets. The data suggest the selective binding of BCG-activated murine macrophages to neoplastic targets triggers the secretion of a potent CF. (Author abstract) (33 Refs)

92. MACROPHAGES AND RESISTANCE TO TUMORS. THE EFFECTS OF TUMOR CELL PRODUCTS ON MONOCYTOPOIESIS.

Farram E, Nelson M, Nelson DS

Kolling Inst. Medical Res., Royal North Shore Hosp., St. Leonards NSW 2065, Australia

J Reticuloendothel Soc; 30(4):259-269 1981

The formation of macrophage colonies from mouse bone marrow cells was inhibited by supernatants from cultures of cells from certain mouse tumors (a methylcholanthrene-induced and a spontaneous sarcoma) human tumors (a melanoma cell line and HeLa cells) and a normal human cell line (Chang) but not by supernatants from normal mouse fibroblasts or EL4 mouse lymphoma cells. The active material had an approx mol wt (by ultrafiltration) of less than 1,000. When the active material was injected iv macrophage colony formation of bone marrow cells taken 3 hr later was impaired. Marrow from old and young mice was equally susceptible. One day after tumor isografting, mice showed depressed colony forming capacity accompanied by monocytopenia; this was followed by increased colony forming capacity and monocytosis about 2 wk later. The substance(s) inhibiting macrophage colony formation appears not to be prostaglandin and not the same as that responsible for the depressive effect of tumor supernatants on cellular inflammatory reactions. (Author abstract) (25 Refs)

93. IN VITRO CYTOCHEMICAL AND CYTOPHYSIOLOGICAL STUDY OF IN VIVO ACTIVATED MOUSE PERITONEAL MACROPHAGES.

Todorutiu C, Mulea R, Daicoviciu D, Risca R

Dept. Experimental Pathology, Oncological Inst., Cluj-Napoca, Romania

Morphol Embryol (Bucur); 27(3):265-269 1981

In vitro morphological, cytochemical and cytophysiological properties of mouse peritoneal macrophages activated in vivo by Corynebacterium parvum and polidin are reported. Macrophages predominated in cultures by 48 hr, showing optimal cell adhesion and spreading. Control macrophages appeared as a mixture of round and spindle-shaped cells. Both C parvum- and polidin-activated macrophages appeared as round spindle-shaped or tripolar large-size cells with a vacuolar cytoplasm. All macrophages were acid phosphatase positive with the Gomori technique, but both treated groups showed significantly higher activity. Control macrophages exhibited a moderate level of phagocytosis toward carbon particles, while polidin- and especially C parvum-activated macrophages showed greately enhanced phagocytosis of carbon particles. (14 Refs)

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY

94. EFFECT OF BCG ON MONOCYTE-MEDIATED ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY IN STAGE I MELANOMA (MEETING ABSTRACT).

Pehamberger H, Holubar K, Knapp W

Department of Dermatology, University of Vienna, Vienna, Austria

Zentralbl Haut Geschlechtskr; 145(4):316 1981

In 20 patients with primary melanoma (11 NM, 9 superficial spreading melanoma) and 15 healthy volunteers, a microassay based on the lysis of 51Cr-labeled antibody-covered human RBC using separated mononuclear cells as effector cells was utilized. All of the melanoma patients were treated by excision with a 5 cm margin and subsequent lymphadenectomy. Ten randomly allocated patients received BCG adjuvant immunotherapy for 9.4 +/-1.7 mo. The av proportion of free 51Cr was significantly less in melanoma patients not treated with BCG than in healthy controls. The number of monocytes counted by means of esterase staining on the other hand was not statistically different. The findings suggest a possible recovery of deficient immune defenses in melanoma patients during adjuvant BCG therapy. (no Refs) (In GER)

95. ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY FOR CULTURED AUTOLOGOUS MELANOMA CELLS.

Livingston PO, Michitsch R, Shiku H, Pinsky CM, Oettgen HF

Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Cell Immunol; 64(1):131-143 1981

Sera from 33 patients with malignant melanoma were tested for antibody-dependent cell-mediated cytotoxicity (ADCC) against cultured autologous melanoma cells prelabeled with [3H]proline in a 36-hr assay. Effector cells (autologous or from normal donors) were obtained by Ficoll-Hypaque separation of peripheral blood. Assay sensitivity (but not specificity) was affected by the effector cells used, the optimal source of effector cells varying between different autologous serum-target cell combinations. The activity of autologous effector cells appeared to correlate inversely with the extent of disease. Sera from 18 patients gave positive direct tests. In seven cases reactivity was strong enough to permit analysis of specificity with absorption tests. Serum from one patient recognized a melanoma antigen restricted to autologous melanoma cells and three other melanoma cell lines, and not present on other melanoma cell lines or autologous tissues, nonmelanoma tumor cells, or xenogeneic cells. Sera from five patients detected a diverse group of widely distributed antigens, all related to fetal calf serum (FCS). Serum from the seventh patient reacted with a widely distributed antigen not related to FCS. (Author abstract) (21 Refs)

96. STUDIES ON THE ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY (ADCC) IN PRIMARY HEPATOMA (MEETING ABSTRACT).

Inagaki Y, Nakamura T, Kumagai N, Watanabe T, Tsuchimoto K, Morizane T, Tsuchiya M
Dept. Internal Medicine, Sch. Medicine, Keio Univ., Shinjuku-ku, Tokyo 160, Japan
Proceedings of the 17th Annual Meeting of Japan Society of Hepatology held in Gifu, Japan, 25-26 June, 1981. Japan Society of Hepatology, Tokyo 113, Japan, 148 pp., 1981.

The ADCC against the hepatoma cells of 15 patients with primary hepatoma diagnosed by angiography etc and that against the cells of 15 healthy individuals were determined. The K cell activity of the lymphocytes in the peripheral blood of the hepatoma patients was measured by 51Cr-release assay using the lymphocytes of healthy individuals having human lymphocyte antigen A2 (HLA A2), which were pretreated with inactivated anti-HLA A2 serum after labeling with 51Cr as the target cells, and the lymphocytes in the peripheral blood of the patients as the effector cells. The K cell activity of the lymphocytes of the hepatoma patients was 4.3 +-2.4% which was significantly lower than that of the healthy individuals, 14.9 +-12.5%. Whether or not ADCC against a cultured human hepatoma cell line (HCC-M) was present in the hepatoma patients was determined by a microcytotoxicity assay using 3H-thymidine postlabeling with the HCC-M pretreated at 37 C for 1 hr with the inactivated patient's serum or healthy person's serum as the target, and the lymphocytes of the peripheral blood of the healthy individuals as the effector. The cytotoxicity of the lymphocytes of the healthy individuals against HCC-M was enhanced by the sera of 7 patients out of 15. This enhancement was significantly depressed when the serum was previously absorbed by HCC-M cells but not by HeLa cells, thus suggesting the presence of ADCC against HCC-M in the serum of the patients. (no Refs) (In JPN)

RELATED BIOLOGY OF IMMUNE CELLS

97. SPONTANEOUS PRODUCTION OF T CELL GROWTH FACTOR BY A CONTINUOUS LINE OF GIBBON TUMOR T CELLS (MEETING ABSTRACT).

Rabin H, Hopkins RF, Ruscetti FW
Frederick Cancer Research Center, Frederick, MD, 21701
In Vitro; 17(3):213 1981

T cell growth factor (TCGF) or Interleukin 2 (IL2) is a lymphokine which supports the in vitro replication of activated T cells. Certain murine and human T cell lines can be activated to produce TCGF by treatment with lectins, phorbol-12-myristrate-13-acetate (PMA) or a combination of lectin and PMA. Some human T cell lines after becoming independent of TCGF have been found to produce levels of TCGF without activation. A continuous T cell line, MLA144, originally established from a gibbon with lymphosarcoma, was found to release spontaneously high levels of TCGF. Conditioned media (CM) from MLA144 cells supports the growth and DNA synthesis of T cells from man, several other species of primates, and from mice. The factor in MLA144 CM has a mol wt, as determined by gel filtration, of 21,500 to 24,000 daltons, elutes from diethylaminoethyl-cellulose at 0.04 to 0.06 M sodium phosphate buffer, pH 7.6, is resistant to 60 C and to low and high pH. MLA144 cells form rosettes with sheep RBC and lack the receptor for the Fc portion of IgG. (no Refs)

98. ESTABLISHMENT AND CHARACTERIZATION OF A CELL LINE DERIVED FROM A PATIENT WITH T-CELL LYMPHOBLASTIC LYMPHOMA. (MEETING ABSTRACT).

Macy ML, Hamburger AW, White CP
Cell Culture Department, American Type Culture Collection, Rockville, MD, 20852
In Vitro; 17(3):225 1981

A new cell line (MARC-I) has been derived from a malignant pleural effusion of a patient with T-cell lymphoblastic lymphoma. The cell line has been in continuous culture for 15 mo and grown in suspension with a doubling x of approx 29 hr. The cells did not require the presence of any exogenous growth factors for their establishment and continued proliferation. The cell line possesses many of the T-cell characteristics of the original cells. Results of histochemical studies on the cell line were similar to the known staining patterns obtained for fresh cells from patients with T-cell neoplasms. The (MARC-I) cells formed rosettes with sheep RBC more efficiently at 4 than 37 C. Approx 10% of the cells exhibited Fc-receptors and 2% of the cells exhibited complement receptors. The cells also expressed HLA antigens and reacted with a monoclonal antibody specific for human T lymphocytes. The following evidence suggests the cells were not derived from normal B lymphocytes present in the pleural effusion. The cells lacked Epstein-Barr nuclear, viral capsid, and early antigens and conditioned medium from the (MARC-I) cells stimulated colony growth of bone marrow cells in soft agar cultures. Moreover, cells from early passages formed colonies in soft agar and produced sc tumors in nude mice. These studies suggest the line was derived from malignant T cells. (no Refs)

99. HOWLER MONKEY-MOUSE T CELL HYBRIDOMAS CARRYING HERPESVIRUS SAIMIRI (HVS) GENOME (MEETING ABSTRACT).

Rangan SR, Martin LN, Gormus BJ
Tulane University, Covington, LA, 70433
In Vitro; 17(3):228 1981

In an attempt to study latency of a primate T lymphotropic herpesvirus, monkey-mouse T cell hybridoma lines have been developed. Cryopreserved HVS genome-carrying splenic lymphocytes (3 x 10(7)) from a howler monkey (Alouatta caraya) with virus-induced lymphoma were fused with 3 x 10(6) BW5147 (TGr) mouse lymphoma cells in the presence of polyethylene glycol 1000. Hybrids were grown as microcultures in a selective medium containing hypoxanthine, aminopterin and thymidine. Cell growth occurred in 38 of 732 wells initiated. While 15 of 35 hybridoma lines tested by rosette formation with aminoethylisothiouronium bromide-treated sheep RBC contained from 10 to 47% rosette-forming cells characteristic of primate T cells, others were negative for such cells. HVS was recovered from 10 of 36 hybridomas tested by co-cultivation with susceptible primate cells. In the virus positive lines, only a small proportion of the cells induced HVS-related cytopathic effect in co-cultures and expressed viral antigens by immunofluorescence. (no Refs)

100. LYMPHOBLASTOID CELLS AS INDICATORS OF LYMPHOKINE GENERATION (MEETING ABSTRACT).

Cochran AJ, Culbert E, Clements G

Surgery and Pathology, University of California, Los Angeles, Los Angeles, CA, 90024

Third International Symposium on Human Lymphokines, October 15-17, 1981, Dallas, Texas Wadley Institutes of Molecular Medicine; 1981

We investigated the migration characteristics of five human lymphoblastoid cell lines, normal human peripheral blood WBC (PBL) and normal mouse spleen cells (MSC). Two lymphoblastoid cell lines (QIMR-WIL and NAMALWA) were actively migratory, as were the PBL and MSC. Migration was metabolically active, reduced at low temperatures and by inhibitors of glycolysis, oxidative phosphorylation and RNA synthesis. The migration of QIMR-WIL cells, PBL and MSC, was inhibited by lymphokine containing supernatants of phytohemagglutinin-pulsed MSC and MSC stimulated by allogeneic cells. The migration of NAMALWA cells was not affected by such supernatants. The lymphokine in the supernatants had properties similar to human WBC-inhibiting factor but distinct from those of macrophage inhibition factor. QIMR-WIL was compared to normal human PBL as indicator cells in the second stage of two-stage lymphokine generation assay (first-stage exposed melanoma patients' or control donors' lymphocytes to formalinized melanoma cells). The QIMR-WIL cells were more sensitive responders and represented an abundant, stable and uniform indicator cell population for two-stage assays. (no Refs)

101. SELECTIVE LYSIS OF NATURAL KILLER (NK) SENSITIVE TARGETS BY A SOLUBLE MEDIATOR (MEETING ABSTRACT).

Wright SC, Bonavida B

Department of Microbiology and Immunology, School of Medicine, University of California Los Angeles, Los Angeles, CA, 90024

Third International Symposium on Human Lymphokines, October 15-17, 1981, Dallas Texas Wadley Institutes of Molecular Medicine; 1981

Soluble mediators released from mitogen activated normal human and murine lymphocytes have been shown to selectively lyse NK target cells. Release was monitored using a miniaturized Marbrook culture system. Significant target lysis required an incubation period of 40 hr when measured by trypan blue exclusion. In man, lysis was obtained against the NK sensitive K562 and MOLT4 targets but not to the NK-insensitive RAJI or IM-9 targets. In the mouse systems, lysis was seen with the NK-sensitive YAC-1 and RL male 1 targets, but not with NK-insensitive targets. Studies with the soluble mediators revealed the following properties: (a) the mol wt is greater than 12,000; (b) stable at-20 C; (c) sensitive to proteolysis; (d) lysis is enhanced by addition of interferon; (e) factors released by purified NK effector cells; (f) release of cytotoxic mediators can be obtained by stimulation with NK sensitive targets; and (g) the cytotoxic factor is adsorbed selectively by NK targets. A good correlation was observed between cytotoxicity measured by direct cell contact in the 51Cr release assay and by the soluble mediator. We propose that NK cytotoxicity may be mediated by soluble cytotoxic factors. (no Refs)

102. SELECTIVE NATURAL KILLER RESISTANCE IN A CLONE OF YAC LYMPHOMA CELLS.

Roder JC, Beaumont TJ, Kerbel RS, Haliotis T, Kozbor D
Dept. Microbiology and Immunology, Queen's Univ., Kingston, Ontario, K7L 3N6, Canada
Proc Natl Acad Sci USA; 78(10):6396-6400 1981

YAC lymphoma cells were treated with the mutagen N-methyl-N'-nitro-N-nitrosoguanidine and then cloned and subcloned. Of 51 clones, 3 were selected for further study. Tenfold more natural killer (NK) effector cells were required to lyse YAC clone 6 and subclone 6-28 cells compared with clone 19 cells of the YAC parent cell line. The max plateau level of cytolysis of the NK-resistant (NKR) variants (20%) never approached that of the NK-sensitive (NKS) variants or YAC parental cells (60%) even after prolonged incubation (20 hr). NKR variants appeared with equal frequency (0.10) on cloning YAC cells that had not been treated with mutagen but these variants were highly unstable with respect to NK sensitivity and were not studied further. Cytolysis of both NKR and NKS lines was mediated by nylon-nonadherent asialo-GM1+ effector cells, and effectors from poly(I).poly(C)-boosted mice preferentially lysed the NKS lines. The NKR alteration did not appear to change the NK target structure (NK-TS): (i) unlabeled NKR cells competed equally with NKS cells in reciprocal unlabeled-target competition assays; (ii) the frequency of target-effector conjugates was identical with NKR or NKS lines; and (iii) normal rabbit serum, which contains antibodies thought to react with the NK-TS, reacted equally against both NKR and NKS targets. The NKR alteration was selective for NK cells and did not result in a resistance to lysis in general; NKR and NKS variants were equally susceptible to (i) cytolysis mediated by alloimmune or lectin-dependent effector T cells and (ii) antibody and complement-mediated lysis. These results are compatible with the hypothesis that the NKR variants have an altered acceptor site on the target cell membrane that normally binds the 'lytic moiety' delivered by the effector cell. (Author abstract) (21 Refs)

103. CLONING CELLS OF THE HUMAN IMMUNE SYSTEM.

Mitchison NA
Tumor Immunology Unit, Univ. Coll. London, Gower St., London WC1E 6BT, England
Haematol Blood Transfus; 26:294-295 1981

Cloning of cells from the immune system provides a means of investigating the workings of the immune system and obtaining insight into leukemia. The main technical problem has been keeping cells alive and multiplying outside the body. B cells have been maintained by the hybridoma technique. T cells have been maintained by use of T cell growth factor or by restimulation of cultures at intervals with antigen. (7 Refs)

104. HUMAN LEUCOCYTE ANTIGENS.

Beverley PC, Linch D, Callard RE
ICRF Human Tumour Immunology Group, Univ. London, University St., London WC1E 6J J, England
Haematol Blood Transfus; 26:309-313 1981

Bone marrow progenitor cells were characterized and stages of T lymphocyte differentiation traced using monoclonal antisera. Bone marrow cells were treated with antimyeloid antibody, which lysed about 50% of the cells, primarily myelocytes and metamyelocytes. After staining with anti-HLe-1 the remaining cells were sorted. Weakly staining cells accounting for less than 2% of total marrow nucleated cells were collected. This fraction contained myeloid and erythroid progenitors and cells with the nuclear enzyme TdT. The TdT-bearing cells were probably lymphoid progenitors and had the phenotype HLe+-TG-1-. About 5% of intrathymic cells were large and lacked the cortical thymic marker HTA-1. The earliest cortical cells lacked HLA-A, -B, and -C antigens, which the presumed marrow progenitor cells possessed. Some early cortical cells possessed TdT and OKT9 markers. Medullary cells resembled peripheral T cells in lacking HTA-1 and TdT but regaining HLA. Thymic phenotypes showed heterogeneity paralleling that shown by leukemic cells, indicating that caution should be used in identifying phenotypes as abnormal. Analysis of peripheral lymphoid cells suggested that UCHT1 antigen is a marker for mature T cells. (17 Refs)

105. CLONES OF MURINE FUNCTIONAL T CELLS.

Hengartner H
Experimentelle Pathologie, Universitat Zurich, Schmelzberstrasse 12, 8091 Zurich, Switzerland
Haematol Blood Transfus; 26:320-322 1981

The generation of alloreactive murine T cells and of cytotoxic T cells against H-Y antigen in mixed lymphocyte cultures is described. Both the alloreactive and cytotoxic cells were cloned in soft agar or under limited dilution conditions. Growth of the cloned cytotoxic cells, unlike that of the alloreactive cells, was dependent on T-cell growth factors. (15 Refs)

106. THE NETWORK CONCEPT AND LEUKEMIA.

Eichmann K
Krebsforschungszentrum - Immunologie, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Haematol Blood Transfus; 26:343-344 1981

Application of the network concept to leukemia is discussed. Network regulation may represent a major mechanism for maintenance of steady state in the immune system. The immune system can be viewed as a series of idiotypic and anti-idiotypic compartments that regulate one another; regulation is determined by effector functions of antigen-specific elements in each compartment. Relevance to leukemia is noted: (1) unbalances in network control make certain lymphocytes susceptible to neoplastic transformation (eg the Balb/c mouse myelomas with antiphosphorylcholine specificity and T15 idiotype), and (2) specific immune therapy could involve recovery of normal T cells from leukemia patients and restimulation in vitro with leukemic cells from the same patient (restimulation methods would seek a high proportion of cytotoxic T cells with specificity for idiotypic determinants on the leukemic cells). The network concept reveals nonspecific manipulation of the immune system to be worthless; only antigen-specific measures could be expected to disturb the balance toward generation of desired effector functions. (3 Refs)

107. COMMITTMENT OF GM-CFU TO GRANULOCYTES IN NUDE MICE BEARING CSF-PRODUCING TUMOR (MEETING ABSTRACT).

Suda T, Miura Y, Ozawa K, Motoyoshi K, Takaku F
Division of Hemopoiesis, Institute of Hematology, Jichi Medical School, Minamikawachi-Machi, Tochigi-Ken, 329-04, Japan
Exp Hematol; 9(Suppl9):159 1981

We observed nude mice transplanted with tumor pieces of lung cancer with prominent leukocytosis. These mice showed a high grade leukocytosis consisting almost exclusively of mature granulocytes. Analysis of the kinetics of hemopoietic stem cells revealed that granulocyte-macrophage colony forming cells (GM-CFC) was increased in the spleen and peripheal blood but not in bone marrow. Tumor-implanted nude mice which showed leukocytosis were used. Sera from tumor-implanted nude mice and tumor-extract were assayed their colony stimulating activity (CSA) using BALB/cA mouse marrow as the target. Serum from these mice showed almost 6 x higher CSA than that of the control nude mice, and 20% of the formed colonies were comprised granulocytes. In the presence of L-cell conditioned medium, known as a macrophage colony stimulating factor (CSF), 30% of colonies were granulocytic on the 7th day of culture. This stimulator formed almost all macrophage colonies (95%) in the culture of marrow cells from control nude mice. In the presence of spleen-cell conditioned medium, 85% of the colonies were granulocytic. These findings show that, in the presence of continuously high level of granulocyte-CSF from the tumor, a part of GM-CFC were committed in vivo into granulocytic cell line and even in the presence of macrophage-CSF they can only differentiate into granulocytes in vitro. The rest of the precursor cells which are still retaining bipotency to differentiate into both granulocyte and macrophage cell line may form either granulocyte or macrophage colonies depending on the nature of CSF. However, there was no colony formation without CSF in the culture of cells from these mice. (no Refs)

CMI METHODOLOGY

108. MORPHOLOGIC STUDIES OF LONG-TERM LEUKOCYTE CULTURES: II: NEW TECHNIQUE FOR DEMONSTRATING ACTIVELY PROLIFERATING TUMOR CELLS FROM PERIPHERAL BLOOD (MEETING ABSTRACT).

Klehr NW, Bretz S, Pott C

Laboratorium Zellbiol, University of Hamburg, Hamburg, W. Germany

Zentralbl Haut Geschlechtskr; 145(4):280 1981

Tumor cell detection in peripheral blood is successful in only a few cases and in any event yields no reliable information respecting metastasis, clinical prognosis, or immunologic status of the host. The authors demonstrate that long-term WBC culture (LLK) not only permits greater probability of tumor cell detection but also enables tumor cell typing, determination of the proportion of proliferating tumor cells, and inferences concerning immunologic status. So as to conform as much as possible to in vivo conditions, no antibiotics were added to the culture medium and the serum aliquot was left to the test system contingent on the thrombocytes. Melanoma patients were studied with this test system. The granulocytes of patients with metastatic melanoma adhered along linear defects in the culture dishes. Tumor cells could easily be distinguished from other cellular components of the culture morphologically. The non-proliferating tumor cells were rosetted with lymphocytes and lost their adhesiveness. Non-proliferating tumor cells of this type were found in instances of distant metastasis. Unfortunately, the description of the technic is quite rudimentary. In addition, it seems to the reviewer that it would be quite difficult to distinguish different types of WBC alongside growing and proliferating tumor cells by bright-field and phase-contrast alone. (no Refs) (In GER)

109. A RAPID METHOD FOR SEPARATING FUNCTIONALLY INTACT HUMAN T LYMPHOCYTES WITH MONOCLONAL ANTIBODIES.

Reinherz EL, Penta AC, Hussey RE, Schlossman SF
Div. Tumor Immunology, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Clin Immunol Immunopathol; 21(2):257-266 1981

In the present study, we exploited a simple adherence technique utilizing monoclonal antibodies to separate highly purified human T-cell subpopulations. Unfractionated T cells were reacted with one of two hybridoma antibodies, termed anti-T4 and anti-T8. The anti-T4 reactive (T4+) subset was previously shown to define the human inducer T-cell subset, whereas the T8+ subset contained suppressor T cells. The monoclonal antibody-coated T cells were separated into adherent and nonadherent fractions based on binding to plastic dishes coated with affinity-purified goat antimouse immunoglobulin. This fractionation resulted in separation of lymphocytes into T4+ and T8+ T-cell subsets by either positive or negative selection. Reanalysis by indirect immunofluorescence indicated that they were greater than or equal to 95% pure. Moreover, in vitro studies showed that the separated populations were functionally intact with regard to proliferative responses and regulatory functions. This procedure should be useful for efficiently and inexpensively separating lymphocytes based on monoclonal antibody binding. (Author abstract) (14 Refs)

110. INTERPRETATION AND IN VIVO RELEVANCE OF LYMPHOCYTOTOXICITY ASSAYS.

Klein E
Tumor Biology Dept., Karolinska Institutet, 104 Stockhom 60, Sweden
Haematol Blood Transfus; 26:345-350 1981

This review deals with human and and murine natural killer (NK) cells, interferon activation of NK cells, generation of NK cells in culture, detection of cytotoxic T cells in the blood of acute infectious mononucleosis patients, in vitro NK cell activity against autologous tumors, and the therapeutic implications of immunologic recognition of such tumors. (32 Refs)

SUPPRESSOR CELL ACTIVITY

111. EVIDENCE FOR TWO DISTINCT POPULATIONS OF SUPPRESSOR CELLS IN THE SPLEENS OF MYCOBACTERIUM BOVIS BCG-SENSITIZED MICE.

Turcotte R
Centre de Recherche en Bacteriologie, Institut Armand-Frappier, Universite de Quebec, Ville de Laval, Quebec H7V 1B7, Canada
Infect Immun; 34(2):315-322 1981

Spleen cells from female C57BL/6 mice infected iv with 1 mg (about 10(7) viable units) of BCG were shown to suppress the blastogenic responses induced by the T-cell mitogens phytohemagglutinin and concanavalin A and by the B-cell mitogen lipopolysaccharide in spleen cells from normal syngeneic mice. By using various separation procedures or cellular treatments, evidence was found for two distinct populations of splenic suppressor cells. One population belonged to the monocyte-macrophage lineage on the basis of their adherence to plastic surfaces, their removal after treatment with carbonyl iron, and their resistance to gamma irradiation. The other population of suppressor cells belonged to the T lymphocytes due to their sensitivity to an anti-Thy 1 antiserum and complement and to gamma irradiation. After separation on nylon wool columns, inhibitory activity was found in both the nonadherent and the adherent spleen cell populations. Both populations of suppressor cells were present in the spleens 14 days after BCG inoculation and persisted for at least 40 days after infection. (Author abstract) (20 Refs)

☆U. S. GOVERNMENT PRINTING OFFICE : 1982—361-547/113

AUTHOR INDEX WITH CITATION NUMBERS

Abe S 70
Adams DO 91
Afanasiev BV 14
Agostini C 12
Akaza H 32
Albertin M 12
Ambrogi F 68
Amos DB 59
Andersen C 18
Anderson SJ 82
Andollina A 75
Antropoli L 20
Babusikova O 3
Bachman AE 2
Bagnara G 11
Bagnara GP 19
Barot-Ciorbaru 55
Battista P 42
Beaumont TJ 102
Bender-Gotze C 77
Bernadou A 17
Bessis M 6
Beug H 79
Beverley PC 104
Biagini G 11
Biagini G 19
Bjorkholm M 25
Blomgren H 81
Boggs D 4
Boller B 46
Bonavida B 101
Bonsi L 11
Bonsi L 19
Borrelli G 20
Bouvet D 64
Braun DP 44
Braun DP 73
Brecher G 6
Breton-Gorius J 4
Bretz S 108
Brezavscek DM 2
Brodt P 53
Brouet JC 5
Bunn PA 37
Burton RC 60
Callard RE 104
Cantrell J 89
Cap J 3
Carbone A 26
Casali P 84
Catinot L 55
Catovsky D 38
Cavalli F 35
Charles A 90
Chedid L 55
Clark EA 85
Clements G 100
Clouse KA 83
Cochran AJ 100
Cohen GI 78
Colamartino P 42
Comis M 19
Copeland CS 82
Cronkite EP 5
Culbert E 100
Daicoviciu D 93
Daugherty DF 61
Davey FR 7
Davis S 28
De The 6
Debre P 5
Dewar AE 24
Di Perna S 42
Di Primio E 42
Dichtel WJ 49
Diehl V 52
Dierckins MS 83
Dillman RO 21
Dresch C 64
Dreyfus B 5
Eichmann K 106
Einhorn S 81
Ellegaard J 30
Elstner E 14
Enders B 34
Eriksson E 54
Evans SR 65
Falcoff E 55
Falk LA 85
Farram E 92
Fauser AA 4
Fejes M 2
Fischer DG 82
Fitzgerald KL 57
Fitzgerald KL 58
Foltinova A 3
Fonatsch C 52
Fouchard M 63
Fox RM 10
Fujiwara H 71
Gallo R 4
Gallo R 5
Gallo RC 37
Gallo RC 6
Gallo RC 80
Gallo RC 9
Garbarino G 11
Gartner S 13
Gasparotto G 12
Gastpar H 43
Gennarelli E 20
Giampietro O 68
Gnasso P 20
Goldstein G 38
Goodwin JS 87
Gordon J 53
Gormus BJ 99
Gottesman SR 56
Graf T 79
Grandjon D 47
Greaves MF 38
Greaves MJ 4
Greaves MJ 5
Greaves MJ 6
Greenberg HM 78
Greenberger JS 78
Grieser S 79
Griffiths JC 21
Gronberg A 54
Guglielmi P 5
Gupta S 40
Haas RJ 77
Haliotis T 102
Hamaoka T 71
Hamburger AW 98
Hanaoka M 16
Hanna N 60
Hansen MM 18
Hansson M 54
Hara T 32
Harfast B 84
Hariri G 38
Harris JE 44
Harris JE 73
Hatano M 86
Hattori N 86
Hattori T 31
Hattori T 72
Hengartner H 105
Hinuma Y 16
Hirai T 72
Hokland P 30
Holm G 25
Holubar K 94
Hopkins RF 97
Horne CH 1
Hosli P 63
Hou-Jensen K 18
Huchet R 47
Huddlestone JR 84
Huh ND 59
Hussey RE 109
Iacopino P 19
Inagaki Y 96
Isaacson P 88
Ito K 29
Itoh O 69
Iwaguchi T 32
Jacob HS 48
Jensen PJ 82
Jin Y 76
Johansson B 25
Johnson DR 74
Johnson HM 65
Johnson WJ 91
Jondal M 74
Jones DB 88
Judd MA 88
Kaluzna W 22
Kalyanaraman VS 37
Kalyanaraman VS 9
Kampert-Blumber 33
Kaplan HS 13
Karcher KH 46
Kato T 62
Kato Y 86
Kay NE 48
Kefford RF 10

Kempf RA 87
Kerbel RS 102
Kiessling R 54
Kim YB 59
Kinoshita KI 16
Kirchner HH 52
Kishimoto T 23
Klehr NW 108
Klein E 110
Knapp W 94
Kobayashi K 32
Kobayashi K 86
Kohmo T 71
Kohno H 31
Kolb HJ 77
Kongshavn P 53
Koren HS 82
Korzeniewska E 79
Koseki K 32
Kozbor D 102
Krajewski AS 24
Kresbach H 36
Krigel R 15
Kristie JA 56
Kumagai N 96
Kung P 38
Kuo S 15
Lafferty WE 87
Lajtha L 4
Lajtha L 5
Lajtha L 6
Langdon WY 51
Lauriola L 26
LeMarbre P 48
Lessels SE 1
Lichtenstein A 89
Liebes L 15
Linch D 104
Livingston PO 95
Macy ML 98
Maeda K 29
Maggiano N 26
Maldini M 75
Marani M 19
Marino M 26
Martin LN 99
Marzo C 20
Masuko Y 70
Matsumoto T 16
Maziere J-C 63
Mazzuca A 75
McCulloch EA 4
McCulloch EA 6
McMaster JS 57
Mellstedt H 25
Merigan TC 84
Mertelsmann R 4
Meserve BL 21
Michitsch R 95
Mickshe M 45
Millward-Sadler 88
Minagawa T 62
Minc J 64
Minna JD 37
Misikova Z 3
Mitchell CE 61
Mitchison NA 103
Miura Y 107
Miyoshi I 16
Mizuno D 70
Mizuochi T 71
Moore MA 4
Morgan DA 63
Morizane T 96
Moser K 45
Motoyoshi K 107
Mulea R 93
Murahata R 89
Musiani P 26
Nagata K 16
Nakai M 16
Nakajima H 70
Nakamura T 96
Nakanishi K 31
Nelson DS 92
Nelson M 92
Neri A 19
Netzel B 77
Nevrla D 15
Newburger PE 78
Niijima T 32
Nobile F 19
Oettgen HF 95
Okumura O 69
Oldstone MB 84
Osato T 27
Osawa T 69
Ozawa K 107
Page PI 90
Pagliardi GL 11
Parker LM 78
Pasquinucci S 20
Payne S 88
Peacock LM 61
Pegoraro L 11
Pehamberger H 94
Pelle E 15
Pelus LM 4
Pembrey RG 66
Penta AC 109
Petit JF 55
Petrini M 68
Pezzutto A 12
Piantelli M 26
Pileri S 33
Pinsky CM 95
Pistone C 42
Pitts AM 61
Plesner T 18
Pluzanska A 22
Pohl A 45
Poiesz BJ 80
Poiesz BJ 9
Poirier O 64
Ponzio NM 57
Ponzio NM 58
Pott C 108
Pretlow TG 61
Pretlow TP 61
Prud'homme JL 5
Rabin H 97
Ralfkiaer E 18
Ralph P 23
Rangan SR 99
Rao J 38
Rasmussen N 41
Reinherz EL 109
Reitz MS 9
Rinehart JJ 48
Risca R 93
Robino A 42
Robinson SH 90
Roder JC 102
Rodt H 77
Ronco F 19
Ross D 4
Ross D 5
Royer-Pokora B 79
Royston I 21
Ruhl H 34
Ruibal Ares B 2
Ruscetti FW 80
Ruscetti FW 9
Ruscetti FW 97
Sacco C 42
Sachs L 6
Said J 78
Saidali MA 14
Sarngadharan MG 37
Sasiain Mdel C 2
Satoh M 69
Schaadt M 52
Schlossman SF 109
Schwarze EW 33
Seligmann M 5
Seligmann M 6
Semenzato G 12
Sendo F 67
Sevenich EA 83
Severi B 19
Shellam GR 51
Shiku H 95
Shimatani N 39
Shirakawa S 16
Shohet SB 6
Sieber G 34
Silber R 15
Stein H 52
Stryckmans P 4
Sturge JC 85
Suda T 107
Takada K 27
Takaku F 107
Takiyama W 72
Taylor IW 10
Terpenning M 89
Theis GA 50
Thierfelder S 77
Thomas Y 47
Thomsen J 41
Thomson AW 1
Todorutiu C 93
Toge T 31
Toge T 72
Tolksdorf G 33
Torikai T 69
Tos M 41
Tripp EH 10
Tsubouchi J 70
Tsuchida T 71
Tsuchimoto K 96
Tsuchiya M 96
Turcotte R 111

Umeda T 32
Unoura M 86
Valvassori L 19
Van Bekkum DW 4
Van Bekkum DW 6
Vargas F 53
Verbi W 38
Vesella R 48
Vitiello N 20
Vogler LB 5
Walford RL 56
Warren HS 66
Watanabe T 96
Wedelin C 25
Weiss R 8
Whisnant CC 91
White CP 98
Wietzerbin J 55
Wilmes E 43
Wilms K 77
Wolf H 43
Wolos JA 7
Wright SC 101
Yamada Y 31
Yamaguchi N 29
Yamazaki M 70
Yanagawa E 31
Zabelina TS 14
Zagury D 63
Zarling JM 83
Zighelboim J 89
Zimmermann A 15

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·CANCERLINE·CANCERLINE·CA
NCERLINE·CANCERLINE·CANCE
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SERIES CB15 No. 82/04

APRIL, 1982

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In this issue:

- EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS.................. 1-41
- EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS.................. 42-56
- EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION.................. 57-93
- THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE.................. 94-102
- RELATED BIOLOGY OF IMMUNE CELLS.................. 103-114
- CMI METHODOLOGY.................. 115-116

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. SEVERE ACQUIRED IMMUNODEFICIENCY IN MALE HOMOSEXUALS, MANIFESTED BY CHRONIC PERIANAL ULCERATIVE HERPES SIMPLEX LESIONS.

Siegal FP, Lopez C, Hammer GS, Brown AE, Kornfeld SJ, Gold J, Hassett J, Hirschman SZ, Cunningham-Rundles C, Adelsberg BR, Parham DM, Siegel M, Cunningham-Rundles S, Armstrong D
Mt. Sinai Medical Center, New York, NY, 10029
N Engl J Med; 305(24):1439-1444 1981

Cellular immunodeficiency associated with chronic perianal ulcerative herpes simplex lesions is reported in four homosexual men. Onset of the disease was characterized by malaise, fever, and wt loss. Later infections included cytomegalovirus,

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Pneumocystis carinii, and Candida albicans. One patient developed Kaposi's sarcoma. Skin anergy, lymphopenia, poor or absent responses to plant lectins and antigens in vitro, and depressed natural killer cell activity against target cells infected with herpes simplex virus were observed. An association may exist between primary cytomegalovirus infection and a particularly prolonged cellular immunodeficiency state. (29 Refs)

2. OPPORTUNISTIC INFECTIONS AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Durack DT
Duke Univ. Medical Center, Durham, NC, 27710
N Engl J Med; 305(24):1465-1467 1981

Current data and theories concerning opportunistic infections and Kaposi's sarcoma in homosexual men are reviewed. Patients are typically young and live in large cities, and many use drugs. Infectious agents are low grade pathogens that often cause opportunistic infections in compromised hosts, and the death rate is very high. The immunodeficiency is cellular rather than humoral, and the gap in host defenses is not limited to those against any one class of microbe. Evidence of previous or current cytomegalovirus infection is a common finding. Kaposi's sarcoma is found in young Africans, elderly Americans, renal-transplant recipients, and homosexual men. The discovery of cytomegalovirus genome in Kaposi's sarcoma tissue indicates the possibility of a cause-effect relationship between the virus and the tumor; some new factor may have distorted the host-parasite relation. Recreational drugs such as amyl nitrite may combine with the effects of persistent viral infection to cause immunosuppression in some genetically predisposed men. (16 Refs)

3. AN OUTBREAK OF COMMUNITY-ACQUIRED PNEUMOCYSTIS CARINII PNEUMONIA. INITIAL MANIFESTATION OF CELLULAR IMMUNE DYSFUNCTION.

Masur H, Michelis MA, Greene JB, Onorato I, Stouwe RA, Holzman RS, Wormser G, Brettman L, Lange M, Murray HW, Cunningham-Rundles S
Cornell Medical Coll., A-431, 1300 York Ave., New York, NY, 10021
N Engl J Med; 305(24):1431-1438 1981

Eleven cases of cellular immunodeficiency associated with Pneumocystis carinii pneumonia are reviewed. Patients were all men (27-40 yr old) who were either drug abusers (7) or homosexuals (6) or both (2). One patient had a cutaneous lesion revealed by biopsy to be Kaposi's sarcoma (KS). One other had angioimmunoblastic lymphadenopathy (AL). Eight patients died. The observed immune dysfunction could have been associated with KS and AL. (35 Refs)

4. PNEUMOCYSTIS CARINII PNEUMONIA AND MUCOSAL CANDIDIASIS IN PREVIOUSLY HEALTHY HOMOSEXUAL MEN. EVIDENCE OF A NEW ACQUIRED CELLULAR IMMUNODEFICIENCY.

Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A
Dept. Medicine, UCLA Sch. Medicine, Center for the Health Sciences, Los Angeles, CA, 90024
N Engl J Med; 305(24):1425-1431 1981

An acquired T-cell immunodeficiency is reported in four previously healthy homosexual men. All patients experienced malaise, fever, and lymphadenopathy for several mo prior to onset of more specific symptoms. All contracted Pneumocystis carinii pneumonia, extensive mucosal candidiasis, and multiple viral infections. Cytomegalovirus was found in the secretions of all patients, and Kaposi's sarcoma developed in one patient 8 mo after he presented with esophageal candidiasis. Antibodies to Epstein-Barr virus and hepatitis B were detected in the other three. Monoclonal-antibody analysis of peripheral blood T-cell subpopulations revealed an inversion of the T helper to suppressor/cytotoxic ratio. The association between chronic cytomegalovirus infection and Kaposi's sarcoma is discussed, and a relationship between the immunodeficiency syndrome and the recent appearance of Kaposi's sarcoma in the male homosexual population is suggested. Cytomegalovirus infection could be a result rather than a cause of the T-cell defect; exposure to an undetected microorganism, drug, or toxin may have made these patients susceptible to infection by opportunistic organisms including cytomegalovirus. (41 Refs)

5. APPLICATION OF A LIVE VARICELLA VACCINE IN CHILDREN WITH ACUTE LEUKEMIA OR NEPHROTIC SYNDROME.

Lin TY, Wang YM, Lin ST
Dept. Pediatrics, Taipei Medical Coll. Hosp., Taipei, Taiwan, Republic of China
J Formosan Med Assoc; 80(7):683-690 1981

Eight children with acute leukemia (AL: 6 acute lymphoblastic and 2 acute myeloblastic) in remission and nine with nephrotic syndrome (NS) were treated with live varicella vaccine. All 17 children were skin test negative for varicella. Seroconversions were demonstrated in all of the six of the AL children who had no detectable antibodies prior to vaccination. Among three AL patients who had a follow-up skin tests 10 mo after vaccination, none became positive. No adverse reactions to the vaccine were observed in the AL children during the 1-yr follow-up. One child, who developed skin rashes on two separate occasions and a fever 18 days after vaccination, was found to have been exposed to varicella near the time of treatment. All of the five NS children who had checked delayed hypersensitivity skin tests showed at least a positive reaction to the antigens tested. Among the nine NS children vaccinated, eight showed serological response 4 wk after vaccination. No adverse effects were observed. One patient developed clinical features compatible with typical varicella 9 mo after vaccination following exposure to a child with varicella. Of 5/9 NS patients in whom follow-up varicella skin tests were performed, only one was positive. The protection provided immunocompromised patients by live varicella vaccine is discussed. (16 Refs)

6. UNUSUAL T-CELL PHENOTYPE IN ADVANCED B-CHRONIC LYMPHOCYTIC LEUKAEMIA.

Matutes E, Wechsler A, Gomez R, Cherchi M, Catovsky D
(c/o Catovsky) M.R.C. Leukemia Unit, Royal Postgraduate Medical Sch., Hammersmith Hosp., Ducane Road, London W12 0HS, England
Br J Haematol; 49(4):635-642 1981

T-lymphocytes isolated by E-rosetting from 22 patients with B-cell chronic lymphocytic leukemia (B-CLL) showed membrane phenotype features distinct from those of normal T-lymphocytes. These changes were particularly marked in advanced disease (Rai Stages II, III, IV and WBC over 100 x 10(9)/l). The most significant finding was the demonstration, in 10 cases, of a major population of E-rosette positive cells (40-80%) unreactive with the OKT monoclonal antibodies against mature or immature T-cells; 15-30% of the cells were unreactive in 7 other cases. A significant reduction in OKT4 positive (helper) lymphocytes was seen in 18 cases. The proportion of

OKT8 positive cells was increased in two and normal or low in the rest. Only four patients with early disease (Stages 0 and I) had a normal T-cell phenotype. These findings could explain abnormalities previously described in the T-lymphocytes of B-CLL and provide new insights into the pathogenesis of the disease. (Author abstract) (19 Refs)

7. COMPARISON OF SOME IMMUNOLOGICAL INDICATORS IN CHILDREN WITH FAVORABLE AND UNFAVORABLE COURSE OF ACUTE LYMPHOBLASTIC LEUKEMIA.

Fabianova J, Mrackova E, Zavazal V

Detska klinika, Lekarska fakulta KU, Marxova 13, 305 99 Plzen, Czechoslovakia

Cesk Pediatr; 36(10):573-575 1981

Immunological indicators were studied in six children (4 boys and 2 girls, 3-12 yr old) with acute lymphoblastic leukemia (ALL), who were in first remission for at least 5 yr, and in eight other children (4 boys and 4 girls, 3-13 yr old) with ALL, who developed recurrences during the first yr of treatment and died 3-4 yr after diagnosis. All patients received remission induction therapy with the combination of prednisone (PR) and vincristine (VCR), methotrexate intrathecally and cranial irradiation, and maintenance therapy with MTX and and 6-mercaptopurine, and cyclic reinduction treatment with PR and VCR. The IgA, IgM, and IgA levels were within the normal range initially in the patients with favorable prognosis, and declined during the first and second yr of cytostatic therapy. While the IgA and IgG levels normalized from yr 3 onward, the IgM level remained low throughout the 5-yr follow-up period. The indicators of cellular immunity, assessed by skin tests and by determining the percentages of T and B lymphocytes, were within the normal range throughout the follow-up period. In the patients with unfavorable prognosis, the immunoglobulin levels were low throughout the follow-up period, and the indicator of cell-mediated immunity sug gested a defect of T lymphocytes. (5 Refs) (In CZE)

8. ABNORMAL LYMPHOCYTES IN X-LINKED LYMPHOPROLIFERATIVE SYNDROME.

Seeley J, Sakamoto K, Ip SH, Hansen PW, Purtilo DT

Dept. Pathology, Univ. Massachusetts Medical Sch., Worcester, MA

J Immunol; 127(6):2618-2620 1981

Helper and suppressor T cells (labeled by OKT4 and OKT8 antisera, respectively,) were studied in males with X-linked proliferative syndrome (XLP), and in their mothers (carriers), asymptomatic brothers, maternally related male cousins (males at risk), and sisters (females at risk). Carrier mothers and both females and males at risk had normal mean percentages of OKT4 and OKT8 cells. However, XLP patients showed significantly lower OKT4 and higher OKT8 percentages compared with healthy controls; abnormally low OKT4:OKT8 ratios were expressed by 6/10 patients with hypogammaglobulinemia and/or lymphoma. Abnormally high OKT4:OKT8 ratios were found in several of 13 males at risk. Among the subjects at risk, OKT4:OKT8 ratios tended to be highest in those who had antibodies to Epstein-Barr virus (EBV) viral capsid antigen but not to EBV nuclear antigen. The ratios may useful in evaluating males at risk for XLP even before they become EBV-seropositive. (24 Refs)

9. DETECTION OF SUPPRESSOR LYMPHOCYTE IN THE BLOOD OF TUMOR PATIENTS BY MEANS OF 3 COMPONENT MIXED LYMPHOCYTE CULTURE.

Govallo VI
Central Inst. Traumatology and Orthopedics USSR Ministry Health, Moscow, USSR
Vopr Onkol; 27(9):30-36 1981

A three component mixed lymphocyte culture was used to identify the suppressor cell activity of lymphocytes in the blood of patients suffering from osteogenic sarcoma, osteoblastoclastoma and lung tumor. The lymphocytes of these patients suppressed the blastogenic reaction of lymphocytes from two unrelated donors. The suppressive activity of the lymphocytes from the patients with bone sarcoma was the strongest. In most cases, a direct correlation was found between the suppressive activities of lymphocytes and serum from the same patients. (Author abstract) (21 Refs) (In RUS)

10. ACUTE LEUKAEMIA, PERSPECTIVES IN DIAGNOSIS AND TREATMENT.

Zwaan FE, Jansen J
Dept. Internal Medicine, Univ. Hosp., Rijnsburgerweg 10, 2333 AA Leiden, Netherlands
Neth J Med; 24(5):190-194 1981

Perspectives in diagnosis and treatment of acute leukemia are reviewed. Advances in cytochemical, immunologic, cytogenetic, and in vitro culture methods allow most centers to identify the neoplastic cell involved in any individual case. One method is the FAB classification for acute non-lymphocytic leukemia (ANLL), based on morphologic features and cytochemical reactions. Antigens detectable by immunofluorescence methods are useful for distinguishing subtypes of acute lymphocytic leukemia (ALL). Presence of the 'common ALL' antigen is correlated with good prognosis, whereas markers for T- and B-cells (sheep RBC receptors) usually indicate poor prognosis. New markers holding promise for differentiation of ALL subtypes include terminal deoxynucleotidyl transferase and the Ia-like antigens. Techniques for culturing normal progenitor cells have aided in the prediction of leukemic relapse; recent development of techniques for culturing leukemic progenitor cells may aid in selecting cytotoxic chemotherapeutic agents. Discovery of the Philadelphia chromosome and other translocations may be useful in cytogenetic diagnosis and determination of prognosis. Excellent results in the treatment of childhood ALL have been achieved with protocols based on 'total therapy,' which include remission induction chemotherapy, CNS prophylaxis with cerebral irradiation, and maintenance chemotherapy. ANLL has a poor prognosis, but modified supportive care has improved therapeutic results. Allogeneic bone marrow transplantation has been of limited success in acute myeloid leukemia. New techniques for prevention or suppression of immunologic interaction between donor and recipient must be evaluated. (26 Refs)

11. THYMIC DYSFUNCTION IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Ershler WB, Ney P, Britt J, Flynn B, Hong R
Vermont Regional Cancer Center, Univ. Vermont, Burlington, VT, 05401
Thymus; 3(4/5):203-212 1981

In order to delineate T-cell function in chronic lymphocytic leukemia (CLL), in vitro lymphocyte function was examined in 25 patients. The response to concanavalin A (con A) and pokeweed mitogen (PWM) was tested in 17 patients; response to phytohemagglutinin (PHA) was tested in 14 patients. Only one patient response was normal for PHA stimulation, one response was normal for con A stimulation, and three responses were normal for PWM stimulation, whether or not the patients had received chemotherapy. In recombination experiments, variable T- and/or B-cell defects as measured by PWM-stimulated proliferation were evident; the data demonstrated that in at least two and possibly three of the four patients tested, T-cell helper function was deficient. In only 2 of 22 patients tested did all three immunoglobulin class determinations fall in the normal range: IgG was normal in 10, IgA in 9, and IgM in 4 of the 22 samples tested. Immunoglobulin biosynthesis in two of four PWM-stimulated cultures was enhanced by incubation over cultured thymic epithelial monolayers. The studies make evident a profound deficiency in the in vitro response to mitogen stimulation in CLL; variable abnormalities in both B- and T-cell function exist in this disease. (23 Refs)

12. OUR EXPERIENCE IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKAEMIA.

Pavlovsky S
Departamento de Onchohematologia, Instituto de Investigaciones Hematologicas, Pacheco de Melo, 3081, 1425 Buenos Aires, Argentina
Sangre (Barc); 26(5B):845-854 1981

We evaluated the results of the different treatment phases (induction, consolidation, CNS prevention and maintenance) in 1,200 acute lymphoblastic leukemias entered from 1967 to 1978 in four consecutive protocols of GATLA and evaluated in April 1981. We can conclude that: (1) WBC count and age are the major prognostic factors to be taken into account in any evaluation; (2) the triple combination DNM-VCR-PRED caused a significant increase in the percentages of complete remissions compared to VCR-PRED alone in children of high risk and adults; no differences were observed in children of low risk; (3) the methods of short consolidation with L-ASP as well as with CTX-AraC did not increase long term relapse free survivals; (4) the use of IT MTX-DMT during induction and maintenance was equally effective to radiotherapy in cranium and IT MTX-DMT in patients with less than 50,000 WBC count and slightly less effective in patients with more than 50,000 WBC count, however, this difference was not significant; (5) the use of daily 6MP and MTX twice weekly produced a significantly better survival free of disease than weekly 6MP and MTX. However, this treatment caused more myelosuppression and immunosuppression with higher percent of infectious episodes and deaths in complete remission; (6) the sequential reinduction treatment with VCR-PRED alternated with CTX-AraC produced a significantly higher survival free of disease in children of good prognosis; (7) levamisole treatment as adjuvant of maintenance chemotherapy caused a significantly higher survival free of disease than the control group, in patients of good and bad prognosis. (Author abstract) (13 Refs) (In SPA)

13. CHEMOIMMUNOTHERAPY FOR MELANOMA WITH DTIC, ACNU, VCR AND OK432: EVALUATION OF NEW COMBINATIONS FOR SURVIVAL RATES, SIDE EFFECTS AND CELLULAR IMMUNITY.

Jimbow K, Yanbe H, Nishio C
Dept. Dermatology, Sapporo Medical Coll., Minami 1, Nishi 16, Sapporo 060, Japan
J Dermatol (Tokyo); 8(4):259-266 1981

The effects of combined chemotherapy [5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, vincristine, and 1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride] and immunotherapy (nonspecific Group A streptococcal preparation OK432) on eight disseminated melanoma patients were evaluated. The patients had primary lesions of histologically verified lentigo-maligna, Stage III or IV; 7/8 patients had lesions belonging to acral and mucosal malignant melanoma and 1/8 had primary occurrence on the back. Controls consisted of 11 Stage III melanoma patients with lentigo-maligna treated by other regimens of chemoimmunotherapy, immunotherapy, radiation, or a combination of these. Survival rates were significantly different at 5 and 8 mo after initiation of treatment from those exhibited by co ntrols; survival period ranged between 5 and 18 mo, including five patients who were still alive. Controls survived 3-15 mo, but all died. Blood picture and liver function tests before and after the trials revealed a decrease in RBC count and increase in serum glutamic oxalacetic transaminase, but the changes were within normal limits. Cellular immunity with specific mitogens of autologous and allogeneic melanoma cells and non-specific mitogens was preserved. Lymphocytes from melanoma patients possessed a high killer cell effect against melanoma cells; the effect was nonspecific as evidenced by the killing of control cells from acute myelocytic leukemia patients. Immunoadjuvant therapy with OK432 appears to affect the cellular immune response in a way similar to BCG. (26 Refs)

14. RAPID EFFECTS OF BCG ON T CELL FUNCTION IN CANCER PATIENTS.

Cannon GB, Reid J, Herberman RB, Connor R, Dean JH, Jerrells T, Perlin E
Dept. Immunology, Litton Bionetics, Incorporated, 5516 Nicholson Lane, Kensington, MD, 20795
Cancer Immunol Immunother; 11(4):265-276 1981

The short-term effects of a single sc injection of BCG on T cell function in cancer patients were studied. Serial blood samples were taken from 48 patients with various cancers and 10 healthy controls. Some patients received 2 x 10(7) or 1 x 10(8) BCG organisms by gun injection. T cell response in all subjects was measured by formation of rosettes with sheep RBC (ERF) and by lymphoproliferative (LP) response to phytohemagglutinin (PHA), purified protein derivative (PPD), and allogeneic cells in mixed lymphocyte cultures. BCG produced a transient increase in ERF and LP response to PPD 3 days after injection. Patients with initially low response to PHA showed an increase on days 3 and 7, while those with initially normal response showed a decrease in response on days 3 and 7. No changes were noted in normal individuals or patients receiving saline or no injections. Apparently BCG has measurable but varied effects on T cell function in some patients. (17 Refs)

15. CORE (2'-5')OLIGOADENYLATE AND THE CORDYCEPIN ANALOG: INHIBITORS OF EPSTEIN-BARR VIRUS-INDUCED TRANSFORMATION OF HUMAN LYMPHOCYTES IN THE ABSENCE OF INTERFERON.

Doetsch PW, Suhadolnik RJ, Sawada Y, Mosca JD, Flick MB, Reichenbach NL, Dang AQ, Wu JM, Charubala R, Pfleiderer W, Henderson EE
(c/o Suhadolnik) Dept. Biochemistry, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Proc Natl Acad Sci USA; 78(11,part2):6699-6703 1981

The 3'-deoxyadenosine (cordycepin) analog of (2'-5')oligo(A) [(2'-5')oligoadenylate with a triphosphate at the 5' end], synthesized enzymatically from cordycepin 5'-triphosphate in lysed rabbit reticulocytes or L-cell extracts was (i) inhibitory to translation in lysed rabbit reticulocytes and (ii) metabolically stable in extracts of either L cells or C85-5C lymphoblasts. The 5' dephosphorylated (core) (2'-5')oligo(A) and the core cordycepin analog can replace human fibroblast interferon in preventing the transformation of human lymphocytes after infection with Epstein-Barr virus B95-8 (EBV) as determined by the decreased incorporation of [3H]thymidine into cellular DNA and the inhibition of morphological transformation of EBV-infected lymphocytes. Whereas the naturally occurring core (2'-5')oligo(A) was cytotoxic to uninfected lymphocytes and proliferating lymphoblasts, the core cordycepin analog was not. Human WBC interferon was more effective than human fibroblast interferon in the inhibition of EBV-induced transformation of human umbilical cord lymphocytes and adult peripheral blood lymphocytes. (Author abstract) (53 Refs)

16. CLINICAL AND IMMUNOLOGICAL STUDY OF 150 CASES OF ADENOCARCINOMA OF THE LUNG.

Pezzuoli G, Roviaro G, Varoli F, Maruotti RA, Zannini P, Sartori F, Calabro F
(c/o Roviaro) Clinica Chirurgica 2a, Ospedale San Paolo, Universita di Milano, Ospedale San Paolo, Via A. di Rudini, 8, 20142 Milano, Italy
Int Surg; 66(3):221-226 1981

An in-depth retrospective statistical analysis was performed on 150 consecutive cases of adenocarcinoma of the lung. One-hundred and twenty-eight patients (85%) underwent pulmonary resection; 15 (10%) had an explorative thoracotomy and 7 (5%) were considered inoperable. At the time of operation, 72 patients were classified as Stage I, 18 as Stage II and 50 as Stage III. Factors analyzed included age, sex, surgical treatment, staging, immunologic monitoring and survival. When compared with other histotypes of our series a statistically significant difference was found in the male:female ratio (less than 0.05), surgical resectability (p less than 0.05), frequency of Stage I, and immunologic status evaluated by studies of delayed hypersensitivity skin tests, lymphocyte blastogenesis, antibody dependent cellular cytotoxicity (ADCC), blocking serum factors and intrastromal peritumoral lymphocyte infiltration. There were no significant differences due to age, cigarette smoking, mediastinal lymph node involvement, except for small oat-cell carcinoma or previous pulmonary diseases. In all stages, the 5-year survival rate was lower for patients affected with adenocarcinoma than for those affected with other histological types, except small oat-cell carcinoma. (Author abstract) (20 Refs)

17. DISTRIBUTION OF FIBROUS LONG-SPACING FIBERS IN NORMAL AND PATHOLOGICAL LYMPH NODES.

Nakanishi I, Masuda S, Kitamura T, Moriizumi T, Kajikawa K
Dept. Pathology, Sch. Medicine, Kanazawa Univ., 13-1, Takara-machi, Kanazawa, 920, Japan
Acta Pathol Jpn; 31(5):733-745 1981

The occurrence and distribution of fibrous long-spacing fibers (FLS) of lymph nodes in normal and pathological conditions have been examined by electron microscopy. The FLS can be easily identified by the characteristic broad cross bands with a 90 to 120 nm period. In normal lymph nodes, the FLS were most often found in the stalk of the valve projecting into the lymphatic sinus and in the perivascular matrix, and less frequently in the wall of the vein, in the sinus wall and in the stroma of the medulla at the hilus. In pathological conditions, a large number of FLS appeared in the hyalinous matrix of lymphocyte depletion type of Hodgkin's disease. These fibers were also observed in reticular matrices of lymphosarcoma and mixed cellularity type of Hodgkin's disease as well as in granulation tissues. It was noted that FLS appeared to be formed in the regions where abundant reticular fibers were laid down. Compared with the ultrastructural and histological findings in various lesions of lymph nodes, the possible mechanism and significance of FLS were discussed. (Author abstract) (37 Refs)

18. EXPRESSION OF RECEPTORS FOR IGA IN HAIRY-CELL AND OTHER B-CELL LEUKAEMIAS.

Lydyard PM, Powell RG, Fanger MW, Worman CP, Cawley JC
Dept. Immunology, Middlesex Hosp. Medical Sch., Arthur Stanley House, 40-50 Tottenham St., London W1P 9PG, England
Br J Haematol; 49(4):643-647 1981

In six cases of both hairy-cell leukemia (HCL) and chronic lymphocytic leukemia (CLL) it was shown that the pathological cells express receptors for the Fc portion of IgA (RFcalpha). Many of the cells simultaneously expressed receptors for IgA, IgM and IgG, and blocking studies showed that these are distinct receptors. In contrast, the malignant cells of most of the various other B-cell leukemias studied showed low levels of RFcalpha expression. The significance of the results is briefly discussed and it is suggested that receptor expression may be a marker of certain stages of B-cell development. (Author abstract) (14 Refs)

19. IMMUNOLOGICAL DISORDERS IN TROPHOBLASTIC DISEASE.

Grinevich IuA, El'chits TV, Alferov AN
Res. Roentgenoradiological and Oncological Inst., Kiev, USSR
Akush Ginekol (Mosk); (9):17-19 1981

States of cellular and humoral immunity were evaluated in 112 patients (18-48 yr old) with trophoblastic tumors (43 had hydatidiform mole, 34 had uterine chorioepithelioma without metastases, and 35 had metastatic uterine chorioepithelioma). The patients received chemotherapy with methotrexate (100-125 mg per course, iv), 6-mercaptopurine (1-2.5 mg/course), vinblastine (50 mg/course), and rubomycin (200-300 mg/course, iv). Prior to being treated, the patients with trophoblastic tumors showed decreases in T- and B-lymphocyte counts, inhibition of leukocyte migration, and dysimmunoglobulinemia. Effective chemotherapy resulted in an increase in T-lymphocyte count, decrease in IgG production, and increase in IgM level. (17 Refs) (In RUS)

20. STUDIES ON LONG-TERM T-CELL-MEDIATED IMMUNITY TO EPSTEIN-BARR VIRUS IN IMMUNOSUPPRESSED RENAL ALLOGRAFT RECIPIENTS.

Crawford DH, Edwards JM, Sweny P, Hoffbrand AV, Janossy G
Human Tumor Immunology Group, Univ. Coll. Hosp. Medical Sch., University St., London WC1E 6JJ, England
Int J Cancer; 28(6):705-709 1981

Peripheral blood lymphocytes from normal seropositive donors and renal transplant recipients on various immunosuppressive regimens have been tested for their ability to mount a cytotoxic response when cultured with autologous EB virus-infected B cells and thereby to cause regression of proliferating B-cell foci. Cultures from 10 normal seropositive donors all showed the normal pattern of regression. Lymphocytes from patients receiving Cyclosporin A therapy with or without prednisolone completely failed to cause regression, thus allowing B-cell lines to proliferate unchecked. Cells from 2 of 17 patients treated with azathioprine and prednisone also failed to cause regression. The cells from the remaining 15 individuals showed regression responses varying from minimal to normal. These results suggest a mechanism by which EB virus-related tumors may arise in immunosuppressed renal allograft recipients. (Author abstract) (34 Refs)

21. IMPAIRED B-LYMPHOCYTE REACTIVITY IN PATIENTS WITH HODGKIN'S DISEASE AND NON-HODGKIN-LYMPHOMAS.

Ruhl H, Enders B, Bur M, Sieber G
Klinikum Steglitz der freien Universitat Berlin, Hematologische Abteilung, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany
Blut; 42(5):271-281 1981

The ability of B cells to differentiate into immunoglobulin-secreting cells (ISC) was studied by a reverse hemolytic plaque assay in 42 patients with Hodgkin's disease (HD) and 33 patients with non-Hodgkin lymphomas (NHL). Forty healthy individuals served as controls. Induction of ISC was triggered by pokeweed mitogen, with optimum response in all groups at concentrations of 1.0-15.0 ul/ml. Mean numbers of ISC (x 10(-2)/10(6) peripheral blood lymphocytes) were 4,370 for HD patients and 2,450 for NHL patients. Mean control value was 10,540. Most HD and NHL patients showed reduced response. No clear correlation between response and patient age could be demonstrated. Response in HD patients decreased with progression of disease, although most patients in remission were still below normal. Coculturing of HD or NHL lymphocytes with normal lymphocytes indicated the NHL response deficiency was due to a B cell defect, T cell function being normal. HD deficiency was due to a B cell defect plus defects in T helper cells and suppressor cells. HD deficiency is evidently reversible and can be corrected with appropriate therapy. (38 Refs)

22. T-CELL SUBPOPULATIONS IN MULTIPLE MYELOMA: CORRELATION WITH CLINICAL DISEASE STATUS.

Oken MM, Kay NE
Hematology Section (111E), Veterans Admin. Medical Center, 54th St. and 48th Ave. S., Minneapolis, MN, 55417
Br J Haematol; 49(4):629-634 1981

T-lymphocyte subpopulations bearing Fc receptors for IgM (Tmu) or for IgG (Tgamma) were studied in blood specimens obtained from 40 normal volunteers and from 16 patients with multiple myeloma. The myeloma patients showed a significant imbalance in T-cell subpopulations characterized by an increase in the percentages of Tgamma cells to 30.0 +-3.9% (mean +- SEM) compared with 12.0 +-3.0% for the controls (p less than 0.001). The patients exhibited a decreased proportion of Tmu cells (13.4 +-4.1%) compared with the control value of 55 +-7% (p less than 0.001). When the results were analyzed according to clinical status it was the patients with indolent or well-controled disease and not those with progressive disease who exhibited an elevated proportion of Tgamma cells. The elevation of Tgamma cells or of a subpopulation of suppressor cells should be further studied as a possible mechanism of disease control in multiple myeloma. (Author abstract) (19 Refs)

23. RELATIONSHIP BETWEEN NATURAL KILLER CELL ACTIVITY AND HISTOLOGICAL FEATURES OF LYMPHOCYTE INFILTRATION AND PARTIAL REGRESSION OF THE PRIMARY TUMOR IN MELANOMA PATIENTS.

Hersey P, Hobbs A, Edwards A, McCarthy WH, McGovern VJ
Medical Res. Dept., Kanematsu Memorial Inst., Sydney Hosp., Sydney, New South Wales 2000, Australia
Cancer Res; 42(1):363-368 1982

A group of 194 melanoma patients with Stage I melanoma was studied in an attempt to correlate histological features of prognostic importance in malignant melanoma with the level of natural killer cell (NK) activity in blood mononuclear cells. Histological features examined were lymphocytic infiltrate of the tumor base, lymphocyte infiltration at the tumor margin, and evidence of partial regression in the tumor. NK activity against melanoma cells and non-melanoma cells was studied in the same patients before and after surgical removal of melanoma. Patients with high NK activity against melanoma and Chang cells had less lymphocyte infiltrate at the base of the tumor irrespective of its thickness than did those with low NK activity. Patients with low NK activity and thin tumors had more lymphocyte infiltration at the base of the tumor than did those with high NK activity. Similar results were obtained in certain subsets of cases with respect to lymphocytic infiltration at the tumor margins and to the presence of partial regression. Although the nature of the association between these histological features and NK activity in blood is unknown, it is suggested that previously unexplained associations between histological features and prognosis may be accounted for by their association with NK activity. If this proves to be correct, measurement of NK activity may be an important additional prognostic factor in patients with melanoma. (Author abstra ct) (29 Refs)

24. T LYMPHOCYTE SUBSETS IN PATIENTS WITH MALIGNANT MELANOMA.

Karavodin LM, Giuliano AE, Golub SH
Div Oncology, Dept. Surgery, UCLA Sch. Medicine, Los Angeles, CA, 90024
Cancer Immunol Immunother; 11(4):251-254 1981

The value of T lymphocyte subset profiles as an indicator of disease progression in malignant melanoma (MM) was studied. Cryopreserved lymphocytes from 57 MM patients and 19 normal individuals were assayed. Monoclonal antibodies were used to identify lymphocyte populations: OKT3.PAN for total peripheral T cells, OKT4.IND for inducer-helper subclass, and OKT8.SUP for suppressor-cytotoxic subclass. Analysis of subset profiles indicated no correlation between any of the subset values and presence or absence of disease, stage of disease, clinical outcome, age, or sex of the patients. A sequential study of three patients with recurrent disease showed no predictable variation of values during the course of the disease. Results indicate no systemic imbalance among T cell subsets in MM. More localized T cell imbalance, such as in lymph nodes adjacent to the tumor, is suggested as a possibility. (19 Refs)

25. DISTURBANCES IN CELLULAR IMMUNITY IN MALIGNANT LYMPHOMA (HODGKIN'S DISEASE.

Burchardt K
Klinika Hematologii, Instytut Chorob Wewnetrznych AM, ul. Szkolna 8/12, 60-967 Poznan, Poland
Pol Arch Med Wewn; 66(2):133-141 1981

Studies on the pathogenesis of immune deficiency in Hodgkin's disease, the consequences of immunological disturbances, and on the role played by immune factors in the pathogenesis of Hodgkin's disease are reviewed. Deficit of T lymphocytes, unspecific spontaneous stimulation of lymphocytes, increased suppressor activity, and intrinsic defect of T-cells are discussed in connection with the pathogenesis of immune deficiency. (50 Refs) (In POL)

26. CYCLOSPORIN A PERMITS THE DISTINCTION BETWEEN SPECIFIC T AND NK ACTIVITY GENERATED IN A HUMAN MLC.

Landegren U, Ramstedt U, Axberg I, Orn A, Wigzell H
Dept. Immunology, Uppsala Univ. Biomedical Center, Box 582, S-751 23 Uppsala, Sweden
Int J Cancer; 28(6):725-730 1981

Human lymphocytes, activated in mixed lymphocyte culture (MLC), express cytolytic activity against a range of target cell types. Cyclosporin A (CyA) efficiently prevents the development of cytotoxic T cells directed against target cells expressing the phenotype of the stimulator cells whilst not preventing an increase in natural killing (NK) activity measured against tumor targets. The drug was further shown not to influence the short-term induction of increased NK activity by interferon. Already established T killer cells are not sensitive to CyA. The drug thus seems to be selectively involved in the induction of immune responses requiring T-cell proliferation. (Author abstract) (27 Refs)

27. EFFECT OF HIGH-CALORIE NUTRITION ON THE IMMUNE POTENTIAL OF PATIENTS WITH GASTRIC CANCER (MEETING ABSTRACT).

Okamoto K, Inawashiro M, Suzuki K, Mori S
First Dept. Surgery, Iwate Medical Univ., Sch. Medicine, Morioka-shi, Iwate Pref. 020, Japan
Geka To Taisha Eiyo; 15(Special):67 1981

Forty-one patients with stage III or IV gastric cancer resected between 1977 and 1980 were divided into the following three groups: Group I was given high-calorie parenteral nutrition of 2,500 cal/day or more beginning shortly after surgery, mainly into the central vein for more than 2 wk; group II was given intermediate-calorie parenteral nutrition of 1,000-2,600 cal/day, after surgery for 5 to 14 days; and group III was given low-calorie parenteral nutrition of mainly water and electrolytes after surgery with no aggressive nutritional supplemented. The pre- and postoperative fluctuation in the WBC count in the peripheral blood, percentage of lymphocytes. Percentage of T cells, purified protein derivative (PPD) id reaction, phytohemagglutinin id reaction, body wt, serum total protein and performance status was determined. The effects on these factors of the oral consumption after surgery were also determined. As the immunological parameters reflecting the improvement of the general state by nutritional control, the PPD id reaction was better than the percentage of lymphocytes or of T cells. The postoperative total serum protein value was markedly improved and the decrease in body wt tended to be inhibited when high-calorie parenteral nutrition was given. High-calorie parenteral nutrition (2,500 cal/day for 14 days or longer) was considered helpful in improving the immune parameters and nutritional state of the gastric cancer patients after surgery. The amount consumed orally by the patients with gastric cancer was presumed to be frequently less than 1,000 cal/day after surgery and to require some nutritional supplement. The WBC count, percentage of T cells, PPD id reaction, total serum protein and body wt were improved in the patients who consumed a lot of food and who had also been given iv parenteral nutrition. (Author abstract) (no Refs) (In JPN)

28. HISTOLOGICAL CLASSIFICATION OF REGIONAL LYMPH NODES IN RELATION TO POSTOPERATIVE SURVIVAL IN PRIMARY LUNG CANCER.

Kitaichi M, Asamoto H, Izumi T, Furuta M
Chest Disease Research Inst., Kyoto Univ., Sakyo-Ku, Kyoto, 606, Japan
Hum Pathol; 12(11):1000-1005 1981

In 129 patients undergoing surgery for primary lung cancer the postoperative prognosis was correlated with the histological features of the regional lymph nodes. The regional lymph nodes were classified according to four patterns: lymphocyte predominance, germinal center predominance, lymphocyte depletion, and unstimulated. The postoperative 3 yr survival rate in Stage 2 and 3 patients with the lymphocyte predominance or germinal center predominance pattern was much better than in those with the lymphocyte depletion or unstimulated pattern (p less than 0.05). (Author abstract) (27 Refs)

29. ABNORMALITIES OF IMMUNOLOGIC RESPONSE OF LYMPHOCYTES IN PATIENTS WITH CANCER OF THE DIGESTIVE ORGANS.

Otsuka S, Mugitani H, Shinbo T, Yata J
First Dept. Internal Medicine, Toho Univ. Sch. Medicine, 6-11-1, Omori-Nishi, Ota-ku, Tokyo 143, Japan
Jpn J Clin Oncol; 11(2):291-298 1981

One hundred and seventy-four patients with digestive tract cancer (28 with esophageal carcinoma, 121 with gastric cancer, 3 with bile duct cancer of carcinoma of the pancreas, and 22 with colorectal carcinoma) not previously treated with chemotherapy were evaluated for lymphocyte function. Percentages of T and B lymphocytes in these patients both before and after surgery did not differ significantly from those of healthy controls. No relationship was found between the percentage of T and B cells and stage of cancer, although the percentage of T cells was lower in 21/1 patients before surgery compared to healthy controls. The percentage of TG cell (IgG) exceeded the normal value of 8% preoperatively in 86 patients, and fell to below 8% in 46 after surgery (from 12.18 before surgery to 7.98 after surgery). An increased percentage of TG cells and a decreased phytohemagglutinin response were observed in 33/90 patients examined with an inverse correlation between these parameters observed for patients with Stage III cancer. An increased percentage of TG cells and a decreased helper activity of T cells were observed in 18.7% of the patients with early stage vs 39% with advanced stage cancer. The significance of changes in these immunologic parameters is discussed. (14 Refs)

30. STUDIES ON CELL-MEDIATED IMMUNITY IN PATIENTS WITH COLORECTAL CANCER: LEUCOCYTE MIGRATION INHIBITION TEST USING ALLOGENIC 3M KCL EXTRACT.

Kojima O, Fujita Y, Iwai N, Yamane T, Kitagawa N, Nishioka B, Majima S
1st Dept. Surgery, Kyoto Prefectural Univ. Medicine, Hirokoji, Kawaramachi, Kamigyo, Kyoto 602, Japan
Aust NZ J Surg; 51(5):434-439 1981

Leukocytes from patients with colorectal and other malignant and non-malignant gastrointestinal diseases as well as those from normal subjects were tested by the leukocyte migration inhibition test (LMIT), employing the method of Clausen, using five different allogenic 3M KCl soluble extracts of colorectal cancer tissue. The normal range of migration index (MI) was found to be greater than 0.82 and less than 1.20 by calculating the mean MI +-2SD of 10 normal subjects with cancer extracts. Mis out of this range were considered to be pathological. In LMIT with a single tumor extract, a pathological MI was found in 46% of 50 colorectal cancer patients, a significantly higher figure than found in the three other groups of patients (4% to 16%). In the panel mode of LMIT, that is, testing each blood sample with five different tumor extracts, 40/50 (80%) of patients with colorectal cancer were reactive, while 2/15 (13%) of gastric cancer patients showed a 'positive' reaction; no positive reactivity was observed in the other two groups of patients. Thus 'positive' reactivity was significantly commoner in patients with colorectal cancer than in patients belonging to the other groups. The frequency of 'positive' reactivity was higher in patients with Dukes C carcinoma than in those with Dukes A or B carcinomas, though differences were not significant. In the follow-up study, marked depression of reactivity was seen 10 to 14 days after curative resection. In patients without recurrence, leukocyte migration was found to be in the normal range during the 2 to 4 wk after surgery. 'Positive' reactivity reappeared in patients with local recurrence. Thus the LMIT, particularly when tested by a panel mode, by demonstrating cell-mediated immunity against tumor-associated antigens of colorectal cancer, provides a method of monitoring colorectal cancer activity. (Author abstract) (13 Refs)

31. GASTROINTESTINAL WORKSHOP.

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Div. Surgical Oncology, Dept. Surgery, R310, Univ. Miami Sch. Medicine, Miami, FL, 33101
Cancer Clin Trials; 4(Suppl):15-18 1981

The immediate and delayed effects of radiotherapy on the gastrointestinal system are reviewed. Late effects include strictures, chronic ulceration, enteritis, fistulae, adhesions, hepatic changes, compromised function of hepatocytes and macrophages, pancreatitis, and diabetes mellitus. Compromised capacity for healing by irradiated tissue is sometimes demonstrated when the tissue is stressed. Most cases of radiation change in the stomach and duodenum have followed irradiation to the paraaortic nodes, pancreas, and the hepatobiliary area. The more common injuries to the small bowel and colon reflect the frequency of cervical carcinoma and the use of radiation in treating rectal carcinoma. Radiation enteritis and colitis become clinically evident 6 mo-2 yr after therapy. Risk factors in the development of radiation-related enteric damage include radiation dose, treatment vol, fractionation pattern, prior surgery, hypertension, thin physique, diabetes mellitus, and pelvic inflammatory disease. (no Refs)

32. IMMUNITY OF PATIENTS WITH LARGE INTESTINE CANCER.

Watanabe T, Higuchi Y, Moritani Y, Iwado T, Matsui T, Hamazaki K, Fuchimoto S, Miwa H, Mannami T, Konaga E, Mimura H, Orita K
First Dept. Surgery, Okayama Univ. Sch. Medicine, Okayama, Japan
Nippon Rinsho; 39(5):42-46 1981

Parameters to study and assess the status of immunity in patients with cancer of the large intestine were discussed. The most basic tests of immunity for patients with large intestine cancer were thought to be cytotoxic T cell (Tc) activity against tumor specific antigen (TSA) and the delayed hypersensitivity initiation T cell response to TSA. Pre- and postoperative Tc tests performed in 107 patients with large intestine cancer showed significant postoperative drops in cytotoxicity indices corresponding to tumor Stages I-IV, but patients with Stage V tumors showed significantly increased cytotoxicity. This increase suggested recurrence or metastasis. Positive macrophage inhibition tests have been observed in large intestine cancer patients to the degree of those observed in patients with gastric cancer. Positive leukocyte inhibition tests have been shown to correlate with high 3-yr survival rates in patients with large intestine cancer; rates of positive leukocyte adherence inhibition tests are correlated with Dukes' classification of large intestinal cancer. Delayed skin response tests correlate with the stage of large intestine cancer and can be used to assess postoperative immune status. Positive purified protein derivative tests correlated to less advanced stages of large intestine cancer. Lymphoblastic transformation tests, peripheral lymphocyte counts, antibody-dependent cell-mediated cytotoxicity tests, natural killer cell activity, blocking factor, and immunosuppressive acid protein have been used to assess the stage of the tumor and/or immune status of patients with cancer of the large intestine. In large intestine cancer patients, the higher the stage of the tumor the lower the non-specific cellular immunity and the greater the amount of immune blocking factors. On the other hand, the higher the stage of the tumor, the lower the specific immunity to TSA. To the degree that immunity is preserved, the prognosis is good. (30 Refs) (In JPN)

33. SERUM FACTORS INHIBITING E-ROSETTE FORMATION IN PATIENTS WITH LUNG MALIGNANCIES.

Saiz-Garcia F, Rodriguez-Valverde V
(c/o Rodriguex-Valverde) Seccion de Reumatologia, Centro Medico Nacional 'Marques de Valdecilla', Santander, Spain
Bull Cancer (Paris); 68(4):346-349 1981

Data supporting the existence of serum factors able to inhibit the formation of RBC (E)-rosettes by peripheral blood lymphocytes (PBL) of 13 patients (mean age 62.5 yr) with lung cancer (3 squamous cell, 2 anaplastic large cell, 3 anaplastic small-cell, 2 alveolar-carcinoma, 1 adenocarcinoma, and 2 unknown) are presented. Seven normal individuals (mean age 47.5 yr) were used as controls. The 13 cancer patients had a low baseline proportion of E-rosetting cells: 40.12 +-6.6% as compared to a normal value of 58.87 +-5.53% (p less than 0.0005). After overnight incubation in medium with 20% fetal calf serum (FCS) or normal pooled AB serum, the proportion of PBL able to form E-rosettes increased to normal levels in 13/13 patients. No such increase was observed in controls. When PBL from cancer patients which had regained the ability to form E-rosettes by incubation with FCS were further incubated with medium containing 20% of heat-inactivated autologous serum, the proportion of E-rosettes dropped to preincubation values. No significant influence on the number of E-rosette forming cells was observed when the sera from cancer patients were used in cultures with normal lymphocytes or with lymphocytes from a different lung cancer patient. In only one case was there a drop in the number of E-rosette forming cells. In this case, both lymphocytes and serum were from patients with cancer of the same histological type. E-rosette deficiency in patients with lung cancer is discussed. (15 Refs)

34. IMMUNITY IN PATIENTS WITH MALIGNANT OVARIAN NEOPLASMS.

Markowska J, Tomaszkiewicz T, Simm S, Jankowiak S
Klinika Onkologii, AM w Poznaniu, ul. Lakowa 1/2, 61-878 Poznan, Poland
Ginekol Pol; 52(8):729-737 1981

Correlations between the E rosette test and seven skin tests (pollen, phytohemagglutinin, purified protein derivative, streptokinase-streptodornase, Candida albicans, dinitrochlorobenzene, and Trychophyton rubrum) were performed in 57 patients with ovarian carcinoma. The E rosette test was performed with tumor-specific antigen in 26/57 patients. Correlation was found between the delayed skin hypersensitivity tests and the E rosette test performed with the tumor-specific antigen. The existence of the correlation suggests the necessity to differentiate the T lymphocytes to subpopulations participating in general and tumor immunity. Both tests give a better insight into the patient's immune status and may be useful in therapy planning. (13 Refs) (In POL)

35. CONCENTRATION OF ROSETTE-FORMING CELLS AND FUNCTIONAL ACTIVITY OF PERIPHERAL BLOOD T-LYMPHOCYTES IN DIFFERENT STAGES OF HODGKIN'S DISEASE.

Loseva MI, Fridliand DIu
Dept. Therapy, Faculty Pediatrics, Medical Inst., Novosibirsk, USSR
Ter Arkh; 53(9):68-71 1981

Functional activity of peripheral blood lymphocytes was studied in 75 Hodgkin's disease patients (56% men, 44% women; median age group, 20-29 yr). Among these patients, 28 had Stage II disease, 28 had Stage III, and 19 had Stage IV. Prior to polychemotherapy, concentrations of T-rosette-forming cells in the Stage II, III, and IV patients were 29.6%, 24.1%, and 19.3%, respectively; macrophage migration indices were 54.9%, 61.3%, and 69.0%, respectively. The contents of B lymphocytes showed progressive increases from 20.1% for Stage II disease to 28.7% for Stage III and 29.5% for Stage IV. Polychemotherapy resulted in certain normalization of the immunological indices; however, during remission, the patients developed secondary imbalance of the content of immunocompetent cells. (8 Refs) (In RUS)

36. INHIBITION OF LEUKOCYTE MIGRATION IN WOMEN WITH OVARIAN CARCINOMA AND ITS DEPEND ENCE ON THE QUANTITY OF LYMPHOCYTES FORMING E-ROSETTES.

Tosner J, Vejbora O, Fixa B
Gynekologicko-porodnicka klinika, Fakultna nemocnica s poliklinikou KUNZ VcKNV, Engelsova 374, 500 06 Hradec Kralove, Czechoslovakia
Cas Lek Cesk; 120(38):1150-1154 1981

Leukocyte migration inhibition (LMI) and the number of E-rosette forming lymphocytes and their possible correlation were studied in 20 women with ovarian carcinoma. Mucinous cystadenopapillary carcinoma was diagnosed in 2 cases, solid undifferentiated carcinoma in 6, and serous cystadenopapillary carcinoma in 12. The migration index (MI) for the entire group was 74.76, and the av percentage of E-rosettes was 40.46%. The MI was 61.8 in patients who had been in remission for at least 3 mo, 80.6 in the patients with progression of the disease ($p = 0.05$), and 85.6 in tumor-free controls. The percentages of E-rosettes were 40.46% in the entire group; 34.61% in the patients with progressive tumor growth, 41.35% in the patients in remission, and 44.0% in the controls, which latter was significantly higher than in the patients with progressive tumor growth. There was no significant correlation between the leukocyte migration inhibition and the percentage of E-rosette forming lymphocytes for the whole group (correlation factor 0.31), but the correlation factor was 0.55 for the patients with progressive tumor growth and 0.52 for those in remission, which suggests the existence of a correlation. (16 Refs) (In CZE)

37. EVALUATION OF DIFFERENT METHODS FOR DETECTING CIRCULATING IMMUNE COMPLEXES. STUDIES IN PATIENTS WITH LUNG CANCER.

Fust G, Fekete B, Angyal I, Jakab A, Pal A, Meretey K, Falus A, Torok K, Szegedi G, Kavai M, Puskas E, Csecsi-Nagy M, Szabo T, Lenkey A, Misz M
Dept. Immunochemistry, Natl. Inst. Haematology and Blood Transfusion, Daroczi ut 24, P.O.B. 44, H-1502 Budapest, Hungary
J Immunol Methods; 46(3):259-276 1981

In a collaborative study involving 7 laboratories, sera from 53 patients with lung cancer, 37 primary and 16 secondary tumors, and sera of 40 healthy blood donors were tested by 19 different assays or assay modifications used for detecting immune complexes. In 12 out of 19 assays, significantly higher immune complex levels were found in the cancer patients than in the healthy subjects. Assays based on interactions between immune complexes and Fc receptors of different cells (lymphocytes, macrophages or platelets) discriminated between cancer patients and healthy subjects and a high percentage (47-87%) of positivity was observed in such assays in patients with lung cancer. In contrast, none of the tests based on immune complex-complement interactions discriminated between cancer patients and healthy subjects. Immunochemical analyses of the PEG precipitates obtained from the sera tested revealed that the concentrations of IgG, IgA and C3 were significantly higher in the precipitates obtained from patients' sera than from control sera, but no significant differences were seen in IgM and C1q concentrations. A 100% correct classification of individuals tested was obtained on discriminant analysis of results with 3 assays: EA rosette inhibition, ADCC inhibition and C3 concentration in PEG precipitates. Correlation between results obtained with individual sera by the different assays was very poor: significant correlation coefficients were found in only 13% of all possible paired comparisons. Our results suggest that Fc receptor-dependent assays are more suitable for detection and measurement of circulating immune complexes in lung cancer than tests based on interactions with complement. (Author abstract) (31 Refs)

38. SUPPRESSOR CELLS FOR NATURAL KILLER ACTIVITY IN CARCINOMATOUS PLEURAL EFFUSIONS OF CANCER PATIENTS.

Uchida A, Micksche M
Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Vienna, Austria
Cancer Immunol Immunother; 11(4):255-263 1981

Suppression of natural killer (NK) cell activity by suppressor cells (SC) in pleural effusions from lung cancer patients was studied. Pleural effusions and peripheral blood were obtained from 40 patients, including 8 with congestive heart failure and 32 with lung carcinoma; samples were also obtained from 33 healthy controls. Pleural effusion mononuclear cells (PEMC) from cancer patients showed little or no NK activity against target K562 erythroleukemia cell lines. Peripheral blood mononuclear cells (PBMC) from normal and cancer patients had NK activity, but this was suppressed in the presence of PEMC from cancer patients. Preincubation of PEMC with PBMC for 24 hr was required for suppression of NK activity. Suppressor cells were found to be Sephadex-G-10-adherent monocytes/macrophages in 21 of the lung cancer patients; in the remaining 4 cases suppressive activity was found in the nylon-wool-nonadherent fraction. Suppression of NK activity was maintained even after suppressor cells were removed, but NK activity was restored within 24 hr of removal of the suppressors. Suppressors apparently affect NK cells by direct prostaglandin-independent interaction. The cytotoxic but not the recognition capacity of NK cells was affected by the suppressor cells. (26 Refs)

39. POPULATIONS OF KILLER CELLS AND T-CELLS BEARING RECEPTORS FOR IGG IN LYMPHOPROLIFERATIVE DISORDERS, WITH SPECIAL REFERENCE TO ADULT T-CELL MALIGNANT LYMPHOMA-LEUKEMIA.

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Jpn J Clin Oncol; 11(2):299-306 1981

Killer T-cells (K) which act as effector cells of antibody-dependent cell-mediated cytotoxicity (ADCC) and of T cells bearing receptors for the Fc portion of IgG (TG) were studied in preparations obtained from patients with peripheral T-cell malignant lymphoma-leukemia (PTML) and other lymphoproliferative disorders. Of the 43 patients studied, 26 had PTML, 5 had mycosis fungoides, 6 had B-cell malignant lymphoma, 1 had null cell malignant lymphoma, 2 had plasma cell dyscrasia, and 3 had multiple myeloma. Fewer K-cells were found in the peripheral blood of patients with lymphoproliferative disorders, while TG cells varied widely in number. Leukemia patients showed significantly fewer K cells than non-leukemia patients. Significant increases in TG cells were observed in some PTML patients. Leukemic cells of patients with adult T-cell leukemia and the tumor cells of lymph nodes had no ADCC activity. (33 Refs)

40. CELLULAR AND HUMORAL IMMUNITY IN HODGKIN'S DISEASE: I. PATIENTS IN CONTINUOUS LONG-TERM REMISSION.

Skovmann-Sorensen O, Schroder H, Moller-Larsen A, Haahr S
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Scand J Haematol; 27(3):171-180 1981

Cell-mediated and humoral immunity to herpes simplex virus (HSV), cytomegalovirus (CMV) and varicella zoster virus (VZV) were examined in 37 patients with Hodgkin's disease in continuous long term remission. This group had lower blast-transformation than a matched control group to all three antigens. Patients originally showing B-symptoms had higher transformation to VZV than those with A-symptoms. Patients treated with irradiation only had higher transformation than those treated with either chemotherapy or a combination of chemotherapy and irradiation. There was a clear tendency towards lower transformation in patients having been in remission for 2 yr or less. Phytohemagglutinin (PHA) stimulation gave lower response in the patient group than in the control group. Patients with B-symptoms had lower response than those with A-symptoms. Interferon production was specially impaired in patients with B-symptoms. The patient group had higher CF titers against HSV and CMV while the control group had higher titers against VZV. B-symptom patients had higher titers against VZV than A-symptom patients. It is concluded that HD patients have impaired immune function many years after discontinuation of therapy, but there are certain differences regarding the in vitro immunity within the patient groups. (Author abstract) (17 Refs)

41. TISSUE AND PLASMA LYSOZYME IN HODGKIN'S DISEASE.

Hansen NE, Clausen PP, Karle H, Christoffersen P
Dept. Medicine, Finsen Inst., Strandboulevarden 49, DK-2100 Copenhagen O, Denmark
Scand J Haematol; 27(3):186-192 1981

Lysozyme positivity in lymph nodes from 33 patients with Hodgkin's disease was examined with an immunoperoxidase technique. Positive reactive histiocytes were found in 18 cases; in 7 cases lysozyme was found also in mononuclear Hodgkin cells and in 3 cases in both reactive histiocytes, mononuclear Hodgkin cells and Reed-Sternberg cells. There was no clear-cut correlation between cellular lysozyme positivity and such feature as histological type, clinical stage and plasma lysozyme. The findings support the theory that the malignant cell in Hodgkin's disease is derived from a lysozyme producing macrophage. The finding that lysozyme positivity was an inconstant feature may reflect both varying functional status of the macrophages and varying differentiation of Hodgkin cells. Increased plasma lysozyme in Hodgkin's disease may stem from both reactive histiocytes, mononuclear Hodgkin cells and Reed-Sternberg cells, but the major part is probably contributed by reactive histiocytes. (Author abstract) (16 Refs)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

42. SUPPRESSION OF NATURAL KILLER (NK) ACTIVITY BY SPLENIC ADHERENT CELLS OF LOW NK-REACTIVE MICE.

Riccardi C, Santoni A, Barlozzari T, Cesarini C, Herberman RB
Inst. Pharmacology, Univ. Perugia, 06100 Perugia, Italy
Int J Cancer; 28(6):811-818 1981

Adherent cells with the ability to inhibit NK activity were found in the spleens of young 8-wk-old SJL/J mice. Such suppressor cells were also found in the spleens of other low-NK-reactive strains, but not in the spleen of age-matched high-NK-reactive strains. These suppressor cells had the characteristics of macrophages, since they were plastic- and nylon-adherent, phagocytosed latex and iron particles, and were resistant to treatment with anti-Thy-1.2 serum plus complement. Their inhibitory activity appeared to be due to their production and/or release of soluble suppressive factor(s). Their suppressor activity was similar to that of pyran copolymer-activated macrophages, which were previously shown to be suppressive for cytotoxicity by NK cells. We suggest here that macrophages may be involved in the physiological regulation of NK activity and may contribute to the low NK activity in some strains of mice. (Author abstract) (25 Refs)

43. QUANTITATIVE STUDIES OF NATURAL IMMUNITY TO SOLID TUMOURS IN RATS. NK ACTIVITY IN ANIMALS WITH PRIMARY OR TRANSPLANTED SPONTANEOUS TUMOURS.

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Cancer Res. Campaign Lab., Univ. Nottingham, University Park, Nottingham NG7 2RD, England, 98104
Int J Cancer; 28(6):747-755 1981

Natural killer (NK) cell activity was measured in a quantitative 6 hr chromium release assay using sarcoma Mc7 cells as targets. The total NK lytic activity present in the spleen and blood of tumor-bearing animals was compared with the corresponding values for age/sex/parity-matched animals. It can be concluded from these studies that: (1) spontaneous tumors do not selectively arise in members of an inbred strain with subnormal NK activity; (2) most large tumors in rats stimulate rather than depress NK activity; (3) early boosting of NK activity by small inocula of tumor cells placed in the mammary pad does not occur with non-immunogenic spontaneous tumors; (4) early boosting of NK activity in the peritoneal site does occur with non-immunogenic tumors, but with a very low frequency. The latter findings suggest that developing spontaneous tumors are unlikely to stimulate the NK system, and emphasize the importance of using syngeneic, spontaneous tumors for studying tumor-host relationships in animals. (39 Refs)

44. THE SPECIFICITY OF RAT NATURAL KILLER CELLS AND CYTOTOXIC MACROPHAGES ON SOLID TUMOR-DERIVED TARGET CELLS AND SELECTED VARIANTS.

Brooks CG, Wayner EA, Webb PJ, Gray JD, Kenwrick S, Baldwin RW
Program in Basic Immunology. Fred Hutchinson Cancer Center, 1124 Columbia St., Seattle, WA, 98104
J Immunol; 127(6):2477-2483 1981

The specificity of rat splenic natural killer (NK) cells and BCG-activated peritoneal cytotoxic macrophages (CMphi) was evaluated. We found that NK cells and CMphi had almost identical specificity. Extensive analysis of the specificity of NK cells showed that tumor lines induced at the same site with the same carcinogen or arising spontaneously in the same tissue could have markedly different NK sensitivities. Cloning experiments revealed that tumor lines were composed of populations of cells with markedly different NK sensitivity, and that variants with altered NK sensitivity could arise spontaneously in cloned lines within a period of mo. Normal fibroblasts were relatively resistant to NK cells, but competition experiments showed that fibroblasts bound NK cells better than did most tumor cell lines. There was a significant correlation between NK sensitivity and susceptibility to hypotonic lysis. In addition, there was also a correlation between NK susceptibility and competitive activity. Cross-competition experiments indicated that there were quantitative rather than qualitative variations in NK cell-binding structures. These studies indicate that three target cell factors determine the specificity of NK cell lysis in solid tumor systems: (1) the amount of NK cell-binding structure expressed on the target cell; (2) a second factor varying between tumor lines, but not between variants of the same line, which seems to be required before cytolysis can be initiated; and (3) the osmotic fragility of the target cell, presumably related to membrane structure or the ability to repair membrane damage. (28 Refs)

45. DETECTION OF NATURAL KILLER CELL-MEDIATED CYTOTOXICITY IN HAMSTERS, USING RAJI TARGET CELLS.

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Clin Immunol Immunopathol; 21(3):332-340 1981

Natural killer (NK) cell-mediated cytotoxicity was investigated in both inbred (CB/SsLak) and outbred [Lak:LVG(SYR)] hamsters. NK cytotoxicity was measured by 51Cr release assay, with mononuclear cells obtained by cardiac puncture used as effector cells and five cell lines (SA-7, Raji, K-562, YAC-1, and IMK101) from various species used as target cells. Positive natural cytotoxicity was observed against SA-7 and Raji cells but not against K-562, YAC-1, or IMK101. Higher cytotoxic indexes were obtained with Raji than with SA-7 target cells. The cytotoxic capacity of NK cells was related to the strain of hamster, the age of the animal, and the effector:target cell ratio. Outbred hamsters exhibited higher NK cytotoxicity than inbred hamsters. Effector cells from hamsters less than 1 mo old had low NK activity. The specificity of the cell lysis was determined by the use of unlabeled competitor cells and 51Cr-labeled target cells. The results suggest that Raji cells are suitable target cells for the study of NK cytotoxicity in hamsters, and that SA-7 and Raji cells may possess common antigenic determinants recognized by hamster NK cells. (Author abstract) (36 Refs)

46. IMMUNOLOGICAL ANALYSIS IN MOUSE NEUROBLASTOMA.

Munakata H, Sasaki M, Morita T, Ebina Y, Aoyama H, Ito S
Second Dept. Surgery, Hirosaki Univ., Hirosaki-shi, Aomori Pref. 036, Japan
Nippon Shonigeka Gakkai Zasshi; 17(4):691-697 1981

The immune response to mouse neuroblastoma (C1300) was analyzed. Cell-mediated immune reactivity of A/J mouse spleen cells against syngeneic neuroblastoma cells was studied by using antibody-dependent cell-mediated cytotoxicity and natural killer (NK) and killer T activity. NK activity of A/J spleen cells against C1300 was of quite a low grade irrespective of age. Killer T activity could be induced by inoculation of C1300 into syngeneic A/J mice. The activity was time dependent, gradually increasing by wk 2 and then decreasing by wk 4. The time course of killer T activity coincided with that of host tumor viability. Rabbit anti-C1300 antibody could be obtained by sc injection of C1300 (2 x 10(7) cells). The specificity was shown to be satisfactory by testing with complement-dependent cytotoxicity and immunofluorescence techniques. (Author abstract) (13 Refs) (In JPN)

47. BONE MARROW TRANSPLANTATION ACROSS THE MAJOR HISTOCOMPATIBILITY BARRIER IN SPECIFIC-PATHOGEN-FREE MICE: EFFECTS OF INTACT VERSUS T CELL-DEPLETED BONE MARROW ON THE EXPRESSION OF ANTI-HOST REACTION IN THE RECIPIENT SPLEENS.

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J Immunol; 127(6):2421-2425 1981

Supralethally irradiated B10.BR (H-2k) strain mice were reconstituted, under barrier-sustained, specific-pathogen-free conditions, with intact bone marrow cells derived from B10 (H-2b) strain mice. Spleens of these chimeras were then examined for reactivities against host (B10.BR) and donor (B10) as well as third-party (B10.D2; H-2d) alloantigens by using a cell-mediated lympholysis (CML) assay in vitro. It is suggested that expansion of the anti-host reactive T cell clones during the first 3 wk after transplantation of intact allogeneic bone marrow may be a key event leading to the manifestation of secondary diseases in allogeneic chimeras maintained under conventional environments. Analysis of CML responses of spleen cells from long-term (6 mo) chimeras indicated some interesting features features: First, the B10-B10.BR chimeras created by using intact bone marrow cells still retained some reactivity against host-type alloantigens when assessed at high effector/target cell (E/T) ratios, whereas B10.BR-B10 chimeras did not.

Second, the fully H-2 incompatible chimeras examined in this study were shown to be competent in generating CML responses as high as those observed in syngeneic chimeras against third-party H-2 alloantigens regardless of whether the donor bone marrow had been depleted of T cells. (Author abstract) (20 Refs)

48. INDUCTION OF LYMPHOMA IN ANTIGENICALLY STIMULATED ATHYMIC MICE.

Baird SM, Beattie GM, Lannom RA, Lipsick JS, Jensen FC, Kaplan NO
Dept. Pathology, Veterans Admin. Medical Center, San Diego, CA, 92161
Cancer Res; 42(1):198-206 1982

Athymic mice infected with pinworms or carrying human tumor xenografts frequently develop a lymphoproliferative disorder which eventually leads to lymphoma. By immunofluorescent analysis of involved tissues, the lymphomas appear to be mixtures of null cells, B-cells, and T-cells. When each lymphoma is established in tissue culture, a predominant cell type grows out. We have now established lymphoma lines of null cells, B-cells, and T-cells. Lymphoma development is preceded by the secretion into the bloodstream of large amounts of murine leukemia virus mol wt 70,000 glycoprotein antigen; however, very little virus is produced. In vivo, the expression of viral envelope antigen appears within a few days after human tumor transplantation and precedes the development of lymphoma by about a mo. Cells expressing viral antigens are first seen in the diffuse cortex of lymph nodes and the periarteriolar white sheath of the spleen, the tissue domains in which lymphomas also first appear. (Author abstract) (21 Refs)

49. INFLUENCE OF PROGRESSIVE GROWTH OF A WEAKLY IMMUNOGENIC FIBROSARCOMA (T 241) ON THE IMMUNE STATUS OF MICE.

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J Cancer Res Clin Oncol; 101(3):265-274 1981

Mitogen-induced lymphocyte proliferation, plaque-forming cell (PFC) response to sheep RBC (SRBC), and cell-mediated lympholysis (CML) were used to monitor immunological changes in C5 7BL/6 mice following implantation of T 241 fibrosarcoma. Initially, the tumor grew locally and then spread to regional lymph nodes. Lung metastases were evident in 80-90% of the animals by day 28. 3H-thymidine incorporation by spleen cells in tumor-bearing (TB) mice was always higher than by normal spleen cells. On day 7, counts were comparable in both normal and TB spleen cells stimulated with Concanavalin A (Con A) and lipopolysaccharide; however, stimulation indices of TB mice spleen cells were significantly reduced with both mitogens. From day 14-28, response to the mitogens fell progressively with increasing tumor size and wt (p less than 0.001). Mixed lymphocyte reaction activity of TB mice spleen cells decreased progressively as the tumor growth advanced. Spleen cells of normal mice generated 63% cytotoxicity was compared to 57%, 44%, 26%, and 17% generated by spleen cells of TB mice taken 7, 14, 21, and 28 days, respectively, after tumor cell inoculation. The values on days 14, 21, and 28 were statistically different from day 0 (p less than 0.001). In TB mice, the level of plaque forming cells (PFC) activity against SRBC was only slightly decreased on day 14. The number of PFC subsequently decreased significantly on days 21 and 28 (p less than 0.001). Sera collected from TB on day 5 produced no inhibition of the response of normal spleen cells to Con A while that collected on days 12 and 20 produced marked inhibition. The possible mechanism of tumor-induced immunosuppression are discussed. (28 Refs)

50. MANIFESTATION AND GROWTH OF TRANSPLANTABLE OSTEOSARCOMA IN MICE: THE EFFECT OF THYMECTOMY AND THYMOSIN TREATMENT.

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Clin Orthop; (159):279-285 1981

The effect of thymectomy and thymosin (TS) treatment on tumor growth, structural appearance and immunity was studied in male CBA mice inoculated with tumor cell suspensions originating from the Dunn osteosarcoma. The mice were divided into five groups (Group I controls, Groups II and IV thymectomized, and Groups III and IV TS-treated) with 15-17 mice/group. In Groups I, III, and IV, the tumor frequency was 80-94%, while in Group II, a significantly higher proportion (p less than 0.001) of mice were tumor free (tumor frequency 47%). Group II also showed the lowest mean tumor wt. No obvious structural differences were found among the tumors of the different groups. However lymphocytic infiltration with a slight admixture of plasma cells was observed at the periphery of Group II tumors. In all groups, very low specific lysis was observed; only at a lymphocyte/tumor cell ratio of 300:1 was a significant difference established. Group II mice showed a higher degree of cytotoxic activity (p less than 0.01) than the rest of the groups. Nor mal animals not subject to tumor cell injections responded in the same apparent magnitude as Groups I, III, and IV. Even extensive immunization produced no measurable increase in lysis. Neither cytotoxic nor growth inhibiting antibodies were found in any of the sera tested. No significant correlation was seen between tumor wt and specific lysis of tumor cells, although the five animals with the highest specific lysis were tumor-free. The results indicated that CBA mice bearing this osteosarcoma did not develop cell-mediated or humoral-immune response against the tumor. (15 Refs)

51. FELINE LEUKEMIA VIRUS-INDUCED ERYTHROID APLASIA: IN VITRO HEMOPOIETIC CULTURE STUDIES.

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Exp Hematol; 9(10):990-1001 1981

Colony forming unit (CFU) assays were developed for feline granulocyte-macrophage (CFUGM), early erythroid (Day 2 CFUE), and late erythroid (Day 7 CFUE) colonies in methylcellulose medium. Feline CFUGM and both Day 2 and Day 7 CFUE were enhanced by feline macrophage conditioned medium and late CFUE often were intimately associated with macrophages. Kittens were inoculated with the Kawakami-Theilen (KT) strain of feline leukemia virus (FeLV) and sequential changes in marrow CFU determined. Erythroid aplasia, characterized by progressive non-regenerative anemia, lymphopenia, and a profound decrease in early and late CFUE but not CFUGM was induced by 3 to 5 wk after FeLV-KT inoculation. The susceptibility of kittens to FeLV-induced erythroid aplasia was strongly age-related; neonatal kittens were most sensitive and substantial natural resistance developed by 4 wk of age. The results demonstrate that FeLV-KT infection induced a rapid and selective suppression of erythroid progenitor cells and represents a suitable model of experimentally-induced acquired erythroid aplasia. (Author abstract) (54 Refs)

52. IMMUNOLOGY OF PYELONEPHRITIS IN THE PRIMATE MODEL. II. EFFECT OF IMMUNOSUPPRESSION.

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Dept. Urology, Delta Primate Center, 3 Rivers Road, Covington, LA, 70433
Invest Urol; 19(3):148-153 1981

Nonobstructive pyelonephritis was produced in the rhesus monkey (Macaca mulatta) by means of retrograde inoculation of Escherichia coli to the point of pyelotubular backflow. The effects of treatment with cyclophosphamide or azathioprine were determined. Commensal renal viruses were not activated by the immunosuppression, and thus did not complicate our results. Both cyclophosphamide and azathioprine prolonged the bacteriuria and produced more severe pathology. Cyclophosphamide decreased the leukocytic response and partially suppressed the antibody response. The increased amount of acute pyelon ephritic lesions after treatment with this drug suggest that the antibody and inflammatory responses may be important protective mechanisms, particularly regarding prevention of abscesses. In contrast, azathioprine did not decrease the leukocytosis nor the antibody responses, but resulted in decreased in vitro responsiveness of lymphocytes to mitogens. The increased severity of chronic pyelonephritic lesions after azathioprine treatment suggests that the cellular immune response also may be an important protective mechanism during the late stages of the disease. The results thus indicate that the immune response is protective and is not directly responsible for the chronic scarring of pyelonephritis. (Author abstract) (28 Refs)

53. CANINE TRANSMISSIBLE VENEREAL SARCOMA: DISTRIBUTION OF T AND B LYMPHOCYTES IN BLOOD, DRAINING LYMPH NODES AND TUMOURS AT DIFFERENT STAGES OF GROWTH.

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Br J Cancer; 44(4):514-521 1981

The levels of T, B and null lymphocytes in the peripheral blood, draining lymph nodes, and tumor masses at different growth stages in dogs transplanted with canine transmissible venereal sarcoma (CTVS) were determined by immunofluorescence techniques. The tumors were classified at excision into 'progressor', 'steady state', and 'regressor' stages of growth. The percentage of B cells in the lymphocytes infiltrating into the progressively growing tumors (n = 10, 37.3 +-7.4%) was significantly higher (p less than 0.025) than that in regressing tumors (n = 21, 26.1 +-1.9%). In contrast, the percentage of T cells in the lymphocytes infiltrating into the regressing tumors (n = 21, 61.2 +-2.6%) was significantly higher (p less than 0.005) than that in the progressively growing tumors (n = 10, 34.0 +-5.1%). The tumors at the steady-state growth stage (n = 9) had 50.8 +-5.7% infiltrating T-cells, which was significantly higher (p less than 0.005) than the progressors and lower (p less than 0.005) than the regressors. The percentage of null cells of progressors (n = 10, 26.0 +-6.9%) was significantly (p less than 0.025) higher than in regressors (n = 21, 13.5 +-2.9%). The draining lymph nodes of progressor dogs (n = 5) had significantly fewer (p less than 0.025) B cells (8.2 +-2.3%) than in normal (n = 5, 16.1 +-3.1%), regressors (n = 12, 19.1 +-1.7%) and steady-state dogs (n = 5, 15.8 +-2.6%). Although there was slight lymphopenia and fluctuation of null cells, no significant differences in T- and B-lymphocyte levels were noted in the peripheral blood of the tumor dogs (n = 44) studied. (Author abstract) (29 Refs)

54. INDUCTION OF CANINE IN VITRO REACTIVITY TO ALLOANTIGEN FOLLOWING INTRALYMPHATIC IMMUNIZATION.

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Bull Cancer (Paris); 68(4):332-337 1981

An experimental model has been developed using the dog to study the induction of systemic cell-mediated immunity following intralymphatic immunization (ILI) with allogenic cells. As detected in one-way mixed lymphocyte cultures, blastogenically-reactive immune peripheral blood lymphocytes were observed after the third ILI with 10(7) cells. The in vitro reactivity was augmented by a fourth ILI to a node not previously injected indicating that a response in one node was followed by the trafficing of memory cells to other nodes. No immune PBL were detected after four ILI with lower doses of 10(3) or 10(5) cells. However, these dogs subsequently responded to a single injection of 10(7) cells with high levels of immune lymphocytes which were detectable for up to 24 days. Apparently, ILI with 10(3) or 10(5) cells, while insufficient to produce detectable levels of alloreactive lymphocytes were sufficient for lymphocyte priming. Results obtained with this model will aid in ongoing human trials of intralymphatic immunotherapy of malignant disease. (Author abstract) (15 Refs)

55. SUPPRESSION OF IMMUNOLOGIC FUNCTION AND DEGENERATION OF LYMPHOID ORGANS IN CYCLOPHOSPHAMIDE-TREATED TURKEYS.

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Am J Vet Res; 42(12):2122-2128 1981

Neonatal administration of 8-20 mg of cyclophosphamide (CY) in turkey poults resulted in a marked alteration in the morphologic features of all major lymphoid organs. Cyclophosphamide induced severe deficiency in antibody response to multiple injections of Brucella abortus and sheep RBC and in vitro proliferative response of peripheral blood leukocytes to concanavalin A. The morphologic regeneration of thymus and of thymus-dependent areas was marked in all major lymphoid organs by posttreatment day 15. This regeneration preceded functional recovery of the mitogenic response of peripheral blood leukocytes. The regeneration of the bursa and bursa-dependent areas in other lymphoid organs was minimal through posttreatment day 27. Thus, CY may be used effectively in turkeys as an immunosuppressive reagent. (Author abstract) (13 Refs)

56. MITOCHONDRIAL ANOMALIES IN RENAL ONCOCYTES INDUCED IN RAT BY N-NITROSOMORPHOLINE.

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Eur J Cell Biol; 25(2):331-339 1981

Renal oncocytes were induced in male Sprague-Dawley rats by oral application of N-nitrosomorpholine (NNM) in concentration of 12 or 50 mg/100 ml drinking water and analyzed by transmission electron microscopy. The oncocytes exhibited mitochondrial anomalies which were very similar to those of human oncocytoma oncocytes. The most striking mitochondrial changes were an unusually large number of the organelles and an excess of the cristae mitochondriales. The shape of the mitochondria varied from round and oval to extremely elongated slender or cup-shaped organelles often piled up to form complex bodies. Rarely large ramifying mitochondria were found. In addition to transversely orientated cristae or tubules the inner mitochondrial membranes frequently formed dense stacks of unusually long cristae often arranged longitudinally. In some mitochondria straight and strictly parallelly arranged neighboring cristae were found to be connected by a paracrystalline array of pillars bridging the mitochondrial matrix. In the majority of oncocytes the mitochondrial matrix contained prominent dense granules (diameter 30-50 nm), but sometimes these were rare or absent. Individual mitochondria of many oncocytes showed membrane-bound deposits of glycogen particles which usually formed rosettes with a diameter of about 80 nm. Partitioned mitochondria were not seen. Often autophagic vacuoles containing portions of degraded mitochondria and dense bodies, probably autophagosomes, were observed. The nature and significance of the oncocytes remains unclear, but we suggest from these and earlier experimental results that oncocytes represent a special type of a neoplastically transformed cell which usually has only a low potential for 'autonomous' growth. Renal oncocytes induced in rats by chemical carcinogens appear to be an excellent experimental model for the further investigation of this cell type. (Author abstract) (46 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

57. VARIATION OF EXPRESSION OF HISTOCOMPATIBILITY ANTIGENS ON TUMOR CELLS: ABSENCE OF H-2KK-GENE PRODUCTS FROM A GROSS-VIRUS-INDUCED LEUKEMIA IN BALB.K.

Schmidt W, Leben L, Atfield G, Festenstein H
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Immunogenetics; 14(3/4):323-339 1981

The antigenic profile of the K-GV tumor of BALB.K origin, induced by Gross virus and maintained in vitro and in vivo, was investigated by serological and immunochemical methods and techniques of cell-mediated immunity. The H-2Kk-gene products were absent by several criteria: (1) monoclonal antibody and conventional alloantisera directed against the H-2Kk antigenic specificities were nonreactive by direct testing and by absorptions. (2) H-2Kk products could not be precipitated from glycoprotein or protein extracts of the radiolabeled K-GV tumor. (3) Cytotoxic effectors against H-2Kk produced by sensitization in vitro and in vivo failed to kill K-GV target cells. (4) The tumor could neither stimulate BALB.B congenic mice to produce cytotoxic effectors nor specific cytotoxic antibody against H-2Kk-gene products. In contrast, the H-2Dk antigen was readily detectable by all these criteria. These findings therefore describe a tumor which has selectively lost the H-2K-gene products. The K-GV tumor was able to generate Gross-virus-specific CTL, but had greatly reduced susceptibility to lysis by Gross-virus-specific CTL generated by H-2K expressing AKR (H-2k) tumors. These findings have important implications for the associative recognition of tumor antigens and the immune surveillance of virally induced tumors. (Author abstract) (49 Refs)

58. IMPORTANCE OF NON-H-2 GENES IN THE CONTROL OF THE IN VIVO GROWTH OF THE VIRUS INDUCED LYMPHOMA YC8.

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J Immunogenet; 8(5):405-413 1981

Differences were found in genetic control of the in vivo growth of the Moloney virus-induced lymphoma YC8 in BALB/c mice and F1 hybrids with various strains having different H-2 haplotypes and/or non-H-2 backgrounds. Mice having the B10 background showed significant resistance to YC8. H-2 genes appeared to play a role in regulating the effect of the B10 background. The C3H background was also able to confer resistance to YC8. In these mice, the H-2 loci seemed to increase the activity of non-H-2 factors. Genes of H-2b and H-2k per se were unable to affect the growth of 10(2) YC8 cells. Genes of the recombinant inbred strain A were ineffective in controlling the growth of YC8. Resistance to YC8 appeared to depend mainly on genes of the background rather than on the major histocompatibility complex (MHC) of the non-BALB/c parent. The hierarchy of resistance among congenic strains was B10RIII greater than B10.BR greater than B10.D2 greater than or equal to B10. The study of backcross mice BALB/c x (BALB/c x B10.BR) showed no linkage between the resistant trait and MHC, sex, or coat color, suggesting that resistance is controlled by at least three unknown non-H-2 genes. When T-cell-deprived resistant mice (ie, BALB/c x B10.BR) were challenged with 10(2) YC8 cells, the frequency of tumor takes was higher than that of controls. Similar results were observed after thymectomy plus irradiation, irradiation alone, or silica injection. The results indicated that the genetic control of resistance to YC8 is mediated both by T cells and macrophage-like cells. (23 Refs)

59. T CELL RECOGNITION OF MOLONEY LEUKEMIA VIRUS PROTEINS: III. T CELL PROLIFERATIVE RESPONSES AGAINST GP70 ARE ASSOCIATED WITH THE PRODUCTION OF A LYMPHOKINE INDUCING 20 ALPHA-HYDROXYSTEROID DEHYDROGENASE IN SPLENIC LYMPHOCYTES.

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J Immunol; 127(6):2565-2570 1981

One of the characteristic cellular immune responses associated with the regression of Moloney leukemia/sarcoma virus-induced tumors is a T cell proliferative response against the major viral envelope glycoprotein, gp70. The results described here demonstrate that associated with this proliferative response is the production of a lymphokine, Interleukin 3 (IL-3). The production of IL-3 was immunologically specific and showed the same specificity as that observed in blastogenic responses. IL-3 production was dependent upon an antigen-specific Thy-1.2+, Lyt-1+, 2-lymphocyte subpopulation but did not require the presence of an Ia+ or an adherent accessory cell. The results also suggested that IL-3 may constitute one of the blastogenic factors previously shown to be involved in the proliferative response to gp70. In particular purified IL-3 was found to induce proliferation of both normal and immune nylon wool purified splenic lymphocytes. The phenotype of the responding lymphocyte subpopulation was Thy-1.2-, Lyt-1-, 2-, Ig-, and Ia-. Maximal IL-3 production occurred approximately 48 hr after the addition of antigen and its production was significantly blocked by mitomycin C. These characteristics were unlike those for the general production of blastogenic factor activity suggesting that IL-3 is responsible for only a minor component of the proliferative response. (Author abstract) (19 Refs)

60. INHIBITION OF T CELL-MEDIATED FUNCTIONS BY MVM(I), A PARVOVIRUS CLOSELY RELATED TO MINUTE VIRUS OF MICE.

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J Immunol; 127(6):2280-2285 1981

A purified preparation of MVM(i), a murine parvovirus closely related to minute virus of mice (MVM), was found to inhibit various functions mediated by murine T cells in vitro. Addition of MVM(i) virus to secondary allogeneic mixed leukocyte cultures resulted in the inhibition of both lymphocyte proliferation (3H-thymidine incorporation) and the generation of cytolytic T lymphocyte activity but not interferon production. MVM(i) virus also inhibited the growth and cytolytic activity of several cloned, long-term Lyt-2+ cytolytic T cell lines. Furthermore, the antigen-induced proliferative responses of parasite- (Leishmania) specific Lyt-1+ T cells in vitro was abrogated by the addition of MVM(i) virus to the culture. Finally, the suppression of an in vitro antibody response to SRBC by MVM(i) virus was the result of the inhibition of T helper cells required for the B cell response. These suppressive effects were specific for MVM(i); parallel studies in which the prototype MVM parvovirus was used showed no significant inhibition in the various systems tested. (Author abstract) (32 Refs)

61. IMMUNE RESPONSIVENESS OF SM/J MICE: HYPER NK CELL ACTIVITY MEDIATED BY NK 1+ QA 5-CELLS.

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J Immunol; 127(6):2391-2395 1981

Compared with other inbred strains, SM/J mice have both abnormally high responses to B cell mitogens and hyper NK cell and K cell activity. This hyper NK cell activity is evident even in older SM/J animals, and a high proportion of SM/J nylon-nonadherent lymphocytes that bind target cells also have lytic activity. The SM/J NK cells are NK 1+, Qa 5-, but H-2v identical B10.SM congenic mice have normal NK activity and NK 1+, Qa 5+ NK cells. Together these results suggest the elevation of NK cell activity in SM/J mice is due to chronic activation or maintenance of a Qa 5-NK cell subset. The genetic control of B cell responsiveness and NK cell activity was examined in (B6 x SM)F1 x B6 backcross progeny and (A x SM)F2 intercross mice. No correlation between NK levels and mitogen responsiveness was detected. NK levels in SM/J mice appear to be under polygenic, non-H-2 gene control. (Author abstract) (41 Refs)

62. SUPPRESSOR CELL ACTIVITY IN TUMOR-BEARING MICE. III. CO-PURIFICATION OF A FACTOR INHIBITING CELLULAR DNA SYNTHESIS AND DNA POLYMERASE ACTIVITY.

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J Immunol; 127(6):2339-2344 1981

The factor(s) derived from fibrosarcoma-induced suppressor T cells was sensitive to pronase and neuraminidase, but not to trypsin, beta-galactosidase, DNase, or RNase. Protein and RNA, but not DNA, synthesis were required to mediate suppression. Suppressor T cell-derived factor(s) could be precipitated by a 50% saturated ammonium sulfate (SAS) solution. The 50% SAS fraction inhibited both in vitro and in vivo spleen cell blastogenesis, whereas the 80% and unprecipitated fractions had no inhibitory activity. Using Sephadex G-200 chromatography, the 2nd protein fraction (Fraction II) contained an inhibitor of both DNA polymerase (IDP) and DNA synthesis (IDS) activity, which possessed no cytotoxic activity. In vitro DNA polymerase alpha activity was suppressed by Fraction II, whereas DNA polymerase beta and gamma activities remained unchanged. Mol wt of IDP/IDS, as determined by Sephadex G-200 gel filtration chromatography, was approx 14,500. Attempts to separate IDP/IDS activities found in Fraction II by anion-exchange chromatography and slab gel electrophoresis were not successful, which suggested that the two activities were the same or very similar molecules. (Author abstract) (26 Refs)

63. NONSPECIFIC IMMUNOSUPPRESSIVE FACTORS IN MALIGNANT ASCITES: FURTHER CHARACTERIZATION AND POSSIBLE RELATIONSHIP TO ERYTHROCYTE RECEPTORS OF HUMAN PERIPHERAL T CELLS.

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J Immunol; 127(6):2300-2307 1981

Nonspecific suppressor factor has been purified from malignant human ascites through partial delipidation, ammonium sulfate precipitation, ACA-22 gel filtration followed by goat anti-human IgG immunoadsorbent chromatography. Mol wt estimated by SDS-PAGE under mild reducing conditions is 50,000 and 25,000 under vigorous reducing conditions. It inhibits PHA, Con A, and PWM responses of peripheral lymphocytes by 50% at microgram concentrations per milliliter in vitro and inhibits plaque-forming cell response to SRBC at 100 ug/mouse in vivo. It also inhibits two-way mixed lymphocyte reactions and natural killer cell activities. It inhibits SRBC rosette formation of peripheral T cells and appears to be an erythrocyte receptor of peripheral T cells. (Author abstract) (56 Refs)

64. MITOGENIC AND CO-MITOGENIC PROPERTIES OF HEMIN.

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J Immunol; 127(6):2469-2473 1981

We report here that hemin, an agent known to induce cellular differentiation in Friend erythroleukemia cells, induces mitogenesis in human T cells and enhances mitogenic responses to supraoptimal concentrations of Con A. Mitogenesis induced by suboptimal or optimal concentrations of Con A is not affected by concentrations of hemin that markedly potentiate responses to supraoptimal amounts of Con A. Maximum mitogenic responses are reached 4 to 5 days after initiation of the cultures. The mitogenic response is macrophage dependent, whereas enhancement of responses to supraoptimal concentrations of Con A is not. Indeed, a greater degree of enhancement is observed after removal of adherent cells. Responses to other mitogens (phytohemagglutinin, wheat germ agglutinin, and sodium periodate) are also enhanced by hemin. Compounds that are metabolically or structurally related to hemin are neither mitogenic nor co-mitogenic. Protoporphyrin IX, which is nonmitogenic, is rendered mitogenic by the chemical insertion of iron to form hemin. Hemin does not affect Con A binding to lymphocytes. These findings indicate that hemin is a macrophage-dependent T cell mitogen with the unusual and remarkable property of overcoming the inhibition of mitogenesis induced by high concentrations of Con A. Since hemin has a limited number of metabolic effects, it provides a useful probe for determination of molecular events associated with lymphocyte activation. (Author abstract) (28 Refs)

65. BINDING OF C-REACTIVE PROTEIN TO HUMAN LYMPHOCYTES: II. INTERACTION WITH A SUBSET OF CELLS BEARING THE FC RECEPTOR.

James K, Hansen B, Gewurz H
Dept. Immunology/Microbiology, Rush Medical Coll., Chicago, IL, 60612
J Immunol; 127(6):2545-2550 1981

In the preceding paper we reported that C-reactive protein (CRP) in the presence of a multimeric binding specificity such as C-polysaccharide (CPS) binds to a small percentage of peripheral blood lymphocytes (PBL). In the present paper additional methods for demonstrating this binding were developed and utilized to help characterize the CRP-binding cell. Heat-modified CRP and E-CPS-CRP each were found to bind to a similar percentage of PBL by microscopic visualization, and an identical degree of binding was observed by cytofluorimetric analysis. Multiple marker studies indicated that CRP-binding cells are found in the T cell, B cell, and null cell categories in a ratio of 2:1:1, respectively. Preferential overlap was seen with IgG FcR-bearing cells, which accounted for 70% of the CRP-binding cells; however, only 12% of the FcR cells bound CRP. These studies indicate that CRP-binding cells predominantly represent a subset of cells bearing FcR, and these cells have the morphologic characteristics of large granular lymphocytes. CRP in the presence of CPS bound to cells of multiple human and murine cultured lines shown to have IgG FcR reactivity, but showed lesser or no binding to cell lines negative for FcR. The precise morphologic and functional characterization of the CRP-binding cells and the nature of the binding site are yet to be established. (Author abstract) (49 Refs)

66. VASOACTIVE INTESTINAL POLYPEPTIDE MODULATION OF LYMPHOCYTE ADENYLATE CYCLASE.

O'Dorisio MS, Hermina NS, O'Dorisio TM, Balcerzak SP
Dept. Medicine, Ohio State Univ., 410 W. 10th Ave., Columbus, OH, 43210
J Immunol; 127(6):2551-2554 1981

Vasoactive intestinal polypeptide (VIP) was found to be a potent stimulator of lymphocyte adenylate cyclase activity. VIP-induced activation of adenylate cyclase was specific for lymphocytes among peripheral blood cells; ie, VIP did not stimulate the adenylate cyclase activity of neutrophils, monocytes, or platelets. The VIP-induced activation of lymphocyte adenylate cyclase was time, temperature, and concentration dependent. VIP and the GTP analog, Gpp(NH)p, acted synergistically to stimulate lymphocyte adenylate cyclase; stimulation by VIP and PGE1 was additive; and VIP activation was antagonized by somatostatin. VIP-mediated activation of lymphocyte adenylate cyclase was observed in normal human T cells, B cells obtained from a patient with chronic lymphocytic leukemia, and a human T cell culture line. The Raji human B cell culture line did possess adenylate cyclase activity, but this activity was not stimulated by VIP. These results suggest that lymphocytes possess functional receptors for VIP and that this peptide may play a role in modulation of lymphocyte function. (Author abstract) (41 Refs)

67. T CELL GROWTH FACTOR RECEPTORS. QUANTITATION, SPECIFICITY, AND BIOLOGICAL RELEVANCE.

Robb RJ, Munck A, Smith KA
Immunology Program, Norris Cotton Cancer Center, Hanover, NH, 03755
J Exp Med; 154(5):1455-1474 1981

T cell growth factor (TCGF) interactions were studied in several cell lines. TCGF bound specifically to receptor sites on activated T cells, producing proliferative response. Unstimulated murine or human lymphocytes and lipopolysaccharide-activated B cell blasts expressed few if any detectable binding sites. Lectin- or alloantigen-activated cells had easily detectable receptors. TCGF-independent T cells did not bind TCGF. (45 Refs)

68. ALTERATION IN SPLEEN LYMPHOID POPULATIONS ASSOCIATED WITH SPECIFIC AMINO ACID DEPLETION DURING L-ASPARAGINASE TREATMENT.

Distasio JA, Durden DL, Paul RD, Nadji M
Dept. Microbiology, Univ. Miami Sch. Medicine, Miami, FL, 33101
Cancer Res; 42(1):252-258 1982

Treatment with antileukemic asparaginases isolated from Escherichia coli and Erwinia carotovora is accompanied by pronounced toxicity and immunosuppression. The capability of three enzymes to hydrolyze L-glutamine and to limit serum levels of this amino acid as well as asparagine has led investigators to hypothesize that glutaminase activity may be responsible for the side effects observed during treatment. We have isolated a glutaminase-free asparaginase with potent antilymphoma activity from Vibrio succinogenes. With this enzyme, we have demonstrated that asparagine depletion alone does not result in suppression of humoral or cell-mediated responses after immunization with sheep RBC. In contrast, treatment with E coli asparaginase abolishes these immune responses. In this study, we investigated the effects of specific amino acid depletion resulting from asparaginase treatment on spleen histology and lymphocyte populations. Administration by ip injection of 50 IU of E coli asparaginase per day for 4 days resulted in a marked reduction in the size of lymphoid follicles within the spleen concomitant with reduced germinal centers. There appeared to be a significant change in reactivity of the germinal centers, evidenced by a decrease in immunoblasts (B-cells). These findings were confirmed by a sensitive peroxidase-anti peroxidase-staining procedure for Ig-containing cells. Examination of lymphocyte subpopulations within the spleen revealed that there was nearly a 40% decrease in the percentage of SIg-bearing cells accompanied by an increase in the ratio of Thy 1.2-bearing cells. The ratio of Lyt-2 to Lyt-1 cells was unchanged as compared to control animals. The data support the hypothesis that glutamine or glutamine combined with asparagine depletion resulting from the treatment of E coli asparaginase causes a marked decrease in spleen lymphocytes of the B-cell lineage. In contrast, asparagine deprivation alone, caused by the administration of the glutaminase-free asparaginase from V succinogenes, does not affect spleen histology or lymphocyte marker distribution. Thus, the asparaginase from V succinogenes should serve as an effective antileukemic agent without causing deleterious effects on the immune system. (Author abstract) (34 Refs)

69. PURINE DEOXYNUCLEOSIDE TOXICITY IN NONDIVIDING HUMAN LYMPHOID CELLS.

Kefford RF, Fox RM
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Cancer Res; 42(1):324-330 1982

Cultured leukemic T-lymphoblasts, incubated in the presence of inhibitors of adenosine deaminase, are exquisitely sensitive to growth inhibition by deoxyadenosine. An analogy between this phenomenon and human combined immunodeficiency disease associated with inborn adenosine deaminase deficiency and the use of inhibitors of adenosine deaminase in the management of T-cell acute lymphoblastic leukemia has been noted. These phenomena are believed to reflect accumulation of high intracellular concentrations of deoxyadenosine triphosphate (dATP) following phosphorylation of deoxyadenosine, inhibiting replicating T-cells. In an attempt to extend these observations to noncultured, nonleukemic T-cells, we studied deoxyadenosine metabolism in human thymocytes. Human thymuses were separated into large replicating and small nondividing cell types by centrifugal elutriation. Both thymocyte subpopulations elevated their dATP pools on incubation with uM concentrations of deoxyadenosine in the presence of erythro-9-[3-(2-hydroxynonyl)]adenosine, an inhibitor of adenosine deaminase. These dATP pool rises were similar in extent to those found in cultured leukemic T-lymphoblasts. However, the finding that small nonreplicating thymocytes elevate their dATP pool was unexpected. This prompted study of unstimulated peripheral blood lymphocytes. These cells (T and non-T) showed a similar elevation of their dATP pool on incubation with deoxyadenosine. Furthermore, these nondividing peripheral blood lymphocytes were killed by uM concentrations of deoxyadenosine in the presence of an inhibitor of adenosine deaminase. The biochemical mechanism of this Go-phase cell death is not known. These findings provide impetus for the investigation of adenosine deaminase inhibitors as lympholytic immunosuppressants or as agents cytotoxic to noncycling malignant lymphoid cells. (Author abstract) (47 Refs)

70. CYCLIC NUCLEOTIDES AND CALCIUM IN HUMAN LYMPHOCYTES INDUCED TO DIVIDE.

Rochette-Egly C, Kempf J
Unite de Recherches 61 de l'INSERM, avenue Moliere, F-67200 Strasbourg, France
J Physiol (Paris); 77(6/7):721-725 1981

Intracellular concentrations of cyclic AMP (cAMP), and cyclic guanosine monophosphate (cGMP) were measured in lymphocytes triggered by concanavalin A, phytohemagglutinin, 12-O-tetradecanoylphorbol-13-acetate and the calcium ionophore A 23187. cGMP rose within min without concomitant cAMP alteration. The cAMP and cGMP levels rose during the prereplicative and replicative phases, respectively. Under calcium depleting conditions, the fluctuations in cAMP and cGMP and increase in (3H)thymidine incorporation into DNA were abolished, suggesting a role for Ca++ in the regulation of lymphocyte proliferation. (21 Refs)

71. PURIFICATION AND CHARACTERIZATION OF AN IMMUNOSUPPRESSIVE FACTOR FROM OVARIAN CANCER ASCITES FLUID.

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Dept. Microbiology, Boston Univ. Sch. Medicine, 80 East Concord St., Boston, MA, 02118
Eur J Immunol; 11(10):780-788 1981

A nonspecific immunosuppressive factor present in malignant (ovarian carcinoma) ascites fluid has been purified by acid extraction from a high mol wt (greater than 200,000) complex followed by preparative isoelectric focusing on Bio-lyte media. It is an acidic protein (pI = 3.6) of mol wt 50,000 to 52,000 as estimated by gel filtration and composed of subunits of 25,000 to 26,000 estimated by sodium dodecyl sulfate polyacrylamide gel electrophoresis, under reducing conditions. It inhibits the phytohemagglutinin-dependent mitogenic response of normal peripheral blood lymphocytes by 50% at 2 ug/ml concentrations in vitro and suppresses 80% of the plaque-forming cell response to sheep RBC at 100 ug per mouse in vivo. Its chemical identity with any of the known plasma proteins has not been established. Its failure to stain with periodic acid Schiff's reagent indicates its minimal content of carbohydrates. It is susceptible to tryptic and pronase digestion but insensitive to deoxyribonuclease and ribonuclease digestion. A smaller suppressive factor identified in the same fluid appears to be a lymphotoxin; it differs from the acid-extracted nonspecific suppressive factor in its lack of susceptibility to trypsin. (Author abstract) (31 Refs)

72. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.

Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
Prostaglandins; 21(5):833-864 1981

The role of prostaglandins (PG) in tumor initiation, promotion, and metastasis is reviewed. Results from tests in Salmonella typhimurium and mice suggest that prostaglandin endoperoxide synthetase (PES) may play a role in activating carcinogenic compounds, such as malondialdehyde, although findings may have been affected by carcinogenic impurities. Arachidonic acid may trigger cooxidation of noncarcinogens, such as benzo[a]pyrene to carcinogenic forms. The kidney may play a role in toxicity or carcinogenicity because of its physiological composition and high blood flow. PES appears to trigger carcinogens when introduced into dog kidneys in vivo. PG may play a role in tumor promotion by tetradecanoyl phorbol acetate (TPA). TPA treatments result in increased PG levels. Nontumorigenic phorbol esters do not increase PG levels. Some inhibitors of PES and lipoxygenases have been found to inhibit tumor growth in mice. PG apparently play a role in proliferation and differentiation of cells and therefore may affect tumor growth. PG appear to inhibit proliferation of monocyte and T lymphocyte precursors and to enhance proliferation of erythrocytes. Manipulation of PG levels may offer a means of controlling tumor growth and metastasis. (161 Refs)

73. INHIBITION OF PURINE NUCLEOSIDE PHOSPHORYLASE BY 8-AMINOGUANOSINE: SELECTIVE TOXICITY FOR T LYMPHOBLASTS.

Kazmers IS, Mitchell BS, Dadonna PE, Wotring LL, Townsend LB, Kelley WN
Dept. Internal Medicine, Sch. Medicine, Univ. Michigan, Ann Arbor, MI, 48109
Science; 214(4525):1137-1139 1981

The guanosine analog 8-aminoguanosine is an effective inhibitor of the purine degradative enzyme purine nucleoside phosphorylase, both in vitro and in intact lymphoid cells. In a human lymphoblast tissue culture system, 8-aminoguanosine, in combination with low concentrations of 2'-deoxyguanosine, causes toxicity toward T cells but not B cells. The selective T cell toxicity correlates with increased accumulation of deoxyguanosine triphosphate in the treated T lymphoblasts. (Author abstract) (16 Refs)

74. SPECIFICITY OF CYTOLYTIC T-CELL RESPONSES.

Burakoff SJ
Sidney Farber Cancer Inst., Boston, MA
The Role of the Major Histocompatibility Complex in Immunobiology. Dorf ME, ed. New York, Garland STPM Press, 406 pp., 1981.

Three aspects of the cytolytic T lymphocyte (CTL) response are reviewed: CTL-target interaction, in which specificity of the CTL response is examined; induction of CTL, wherein antigen requirements for generation of the CTL response is considered; and modulation of the CTL response, where evidence for the existence of helper and suppressor T cells that interact with prekiller cells is presented. Methods employed in studying CTL are described. (116 Refs)

75. BIOCHEMICAL PROPERTIES OF DIFFERENTIATION FACTORS FOR MURINE MYELOMONOCYTIC LEUKEMIC CELLS IN ORGAN CONDITIONED MEDIA - SEPARATION FROM COLONY-STIMULATING FACTORS.

Nicola NA, Metcalf D
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J Cell Physiol; 109(2):253-264 1981

Various murine (C57BL/6f/J/WEHI) organs were surveyed for their capacity to synthesize and release differentiation factor (DF) into the medium. The effect of prior injection of endotoxin (5 ug) on DF production was studied and the biochemical properties of DF produced under various conditions were compared with each other and with the DF found in the serum. Optimal strategy for purifying DF was described, with particular attention given to its separation from the proliferative stimulus colony-stimulating factor (CSF). All organs could induce differentiation of the myelomonocytic leukemic cell line s WEHI-3B, but were much more effective from endotoxin-injected animals. Production of DF was dependent on protein synthesis and occurred throughout the 7-day incubation period. DF produced by the different organs in vitro and found in vivo in endotoxin serum could be distinguished from the majority of granulocyte-macrophage (GM) and macrophage (M) CSF. DF was precipitated by 55% ammonium sulfate and did not bind to Concanavalin A-Sepharose; CSF required 85% saturation and bound to Concanavalin A-Sepharose. DF eluted later than CSF from Phenyl-Sepharose columns. DF could be distinguished from M-CSF by its apparent mol wt on native gels, but could not be distinguished from GM-CSF (23,000 on that basis). DF appears to be a 23,000 (approx) mol wt protein which is different from GM-CSF and may or may not be a glycoprotein. (26 Refs)

76. VARIATION OF INTERFERON INDUCTION AT THE BONE MARROW LEVEL. STUDIES ON INTERFERON INDUCTION IN RELATION TO NATURAL CELL-MEDIATED CYTOTOXIC MECHANISMS.

Orn A, Gidlund M, Wigzell H, Gresser I
Dept. Immunology, Uppsala Univ. Biomedical Center, Box 582, S-75123 Uppsala, Sweden
Eur J Immunol; 11(10):795-799 1981

The effects of interferon inducers on different cytolytic mechanisms were studied in the high leukemia mouse strain AKR. A clear depression in baseline cytolytic potential and interferon-mediated stimulation of natural killer cell activities was demonstrated. This depression was most pronounced after 8 wk of age. In contrast, antibody-dependent, cell-mediated cytotoxicity against IgG-coated chicken RBC was always normal. Bone marrow chimeras between CBA and AKR mice were produced to investigate the influence of bone marrow vs host-mediated factors in these two strains with regard to interferon induction and cytolytic functions. Bone marrow genotype was found to be the dominating factor with regard to both parameters. Mice reconstituted with AKR bone marrow were deficient both in interferon production using tilorone and Newcastle disease virus as inducers, and at the level of natural killer cells responding to exogenously administered interferon. The possible relationship between these findings and the development of lymphomas in AKR mice is discussed. (Author abstract) (32 Refs)

77. INTERFERON-INDUCED NK AUGMENTATION IN HUMANS. AN ANALYSIS OF TARGET RECOGNITION, EFFECTOR CELL RECRUITMENT AND EFFECTOR CELL RECYCLING.

Ullberg M, Merrill J, Jondal M
Dept. Tumor Biology, Karolinska Institutet, Stockholm, Sweden
Scand J Immunol; 14(3):285-292 1981

By combining a single-cell cytotoxicity assay in agarose with estimations of the max natural killer (NK) cell potential (Vmax) by 51Cr release, the mechanisms behind interferon augmentation of human NK cells were analyzed. The number of target-binding cells (TBCs) the fraction of active TBCs, and NK cell recycling were studied after short-term interferon treatment. The results demonstrate a dual effect of interferon on human NK cells: effector cell recruitment and increased effector cell recycling. Both of these variables were increased when NK cells were tested against the standard target K-562 and against Daudi and BJAB cells, derived from B-type lymphomas. However, when T cell lines derived from acute lymphocytic leukemia (Molt-4 and 1301) were used as targets, a larger fraction of active NK cells were found among untreated TBCs, whereas interferon treatment only resulted in increased effector cell recycling and not in effector cell recruitment. No increase in TBCs after interferon treatment could be detected with any cell line tested. The difference seen between T and non-T cell lines with regard to interferon-induced effector cell recruitment is discussed in relation to known characteristics of the human NK system. (Author abstract) (32 Refs)

78. TUMOR IMMUNITY AND THE MHC.

Greene MI
Harvard Medical Sch., Boston, MA
The Role of the Major Histocompatibility Complex in Immunobiology. Dorf ME, ed. New York, Garland STPM Press, 406 pp., 1981.

Major histocompatibility complex genes involved in the host response to tumor antigens are described. Topics include cellular interactions in syngeneic tumor immunity, genes responsible for tumor resistance, H-2 complex and hybrid resistance, genetics of natural killer cells and tumor immunity, relationship of tumor antigens to the H-2 complex, genetic regulation of immune response to tumor antigen, synthesis of genetic influence on tumor immunity, modulation of immune response by genetically defined antisera, and effect of anti-I-A alloantisera on tumor immunity. (73 Refs)

79. THE ROLE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX IN IMMUNOBIOLOGY.

Dorf ME
Harvard Medical Sch., Boston, MA
The Role of the Major Histocompatibility Complex in Immunobiology. New York, Garland STPM Press, 406 pp., 1981.

Products of the major histocompatibility complex (MHC) and their functions, structure, and genetic control are discussed. The MHC is able to mount specific immune responses to distant thymus-dependent antigens, develop mixed WBC reactions in culture, regulate immune responses by controlling essential antigen-dependent cellular interactions of the immune system, develop specific suppressor T cells, and interact with the complement system. Topics discussed include the genetic fine structure of the mouse H-2 gene complex, antigens of the TLA region of the mouse genome, genetics and biology of the human leukocyte antigen system, biochemical analysis of MHC products, complement and the MHC, genetic control of immune responsiveness, cellular interactions, role of the MHC in delayed type hypersensitivity, specific T cell factors with MHC determinants, specificity of cytolytic T cell responses, and tumor immunity and the MHC. (1478 Refs)

80. MAJOR HISTOCOMPATIBILITY COMPLEX CONTROL OF THE IDIOTYPIC NETWORK IN THE MOPC 173 SYSTEM.

Boyer C, Schiff C, Milili M, Fougereau M
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Eur J Immunol; 11(10):769-776 1981

Regulation of the anti-idiotypic response against MOPC 173 (M-173) was studied after syngeneic and allogeneic immunizations. The immunogen was M-173 polymerized with glutaraldehyde, and hemagglutinating titers (HT) were determined with sheep RBC M-173. H-2 regulation of the response was clearly shown in mice having the same Igh-Ca genes as the immunogen protein. H-2a mice (BALB/c) are dispersed responders and 30% did not respond. H-2k mice (BALB.K) are high responders and H-2b mice (BALB.B) are nonresponders. In animals of a non-BALB background, similar observations were made. More dispersed HT values for the C58 animals as compared with those of the BALB.K suggest that a second level of regulation by background genes might be superimposed. When alloimmunization was used in strains not expressing the Igh-Ca allotype, animals responded whatever the H-2 haplotype. In this case, allotypic determinants might play a carrier role. All responder mice consistently made anti-idiotypic antibodies. BALB.B (and BALB/c) mice are responders to U-10, polymerized with glutaraldehyde and can respond to the M-173 idiotype when they are immunized with M-173 coupled to a heterologous carrier (Kle). The unresponsiveness of BALB.B mice to M-173 is thus idiotype-specific and is not due to a defect in the anti-idiotypic antibody repertoire. Injection of M-173 before M-173-Kle prevents the response to M-173 but not to Kle, which favors the occurrence of suppressive T cells. Since F1 animals between BALB.B and B10.A (3R), (4R) or (5R) are all nonresponders, genes involved in the response to M-173 are not in the K, I-A, I-J, or I-E subregions. A participation of the I-B subregion or an I-A + I-E/C complementation cannot be excluded. (48 Refs)

81. T-CELL GROWTH FACTOR (INTERLEUKIN 2) AND TERMINAL TRANSFERASE ACTIVITY IN HUMAN LEUKEMIAS AND LYMPHOBLASTIC CELL LINES.

Mertelsmann R, Gillis S, Steinmann G, Ralph P, Stiehm M, Koziner B, Moore MA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blut; 43(2):99-103 1981

Mononuclear blood cells from 49 adult patients with various types of leukemia (13 ALL: acute lymphoblastic; 17 ANLL: acute non-lymphoblastic; 2 CML: chronic myeloid, chronic phase; 7 CML-blast crisis; 3 CLL: chronic lymphocytic; 5 LSA: lymphosarcoma; and 2 HCL: hairy cell), three patients with non-hematological malignant tumors, and healthy volunteers were examined in assays testing mitogen-induced proliferation and T-cell growth factor (TCGF: interleukin 2) production and response. Spontaneous proliferation of normal lymphocytes was characteristically low (104-306 cpm incorporated in unstimulated medium control cultures). Nonstimulating cultures did not produce detectable amounts of TCGF. Phytohemagglutinin (PHA)- or concanavalin A (Con-A)-stimulated cultures produced greater than 0.5 U/ml of TCGF. Of 20 patients (9 ALL, 7 ANLL, and 4 CML-blast crisis) exhibiting high levels of terminal deoxynucleotidyl transferase (TdT), 19 showed increased proliferation and high TCGF levels following PHA and Con-A stimulation. 3H-thymidine incorporation decreased in most TdT(+) leukemias decreased in response to with purified human TCGF and PHA when compared to PHA-stimulated proliferation. Costimulation with purified TCGF and PHA produced significantly increased proliferation in control lymphocytes and in TdT(-) leukemias (ANLL, LSA, CLL, and HCL). No TCGF production or response was seen in 2/2 cases of TdT(-) ANLL, in 2/2 TdT(-) CML, in 3/3 TdT(-) CML-blast criss, and in 1 TdT(-) LSA. All other cases studied were TdT(-) and revealed an essentially normal pattern of TCGF production. The data suggested that aberrant proliferation and lack of maturation in these leukemias may be associated with or result from breakdown in cell-mediated control of proliferation. (11 Refs)

82. NK CELLS, ANTI-TUMOR SURVEILLANCE AND INTERLEUKINS.

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Immunol Today; 2(11):205-208 1981

A common set of goals are suggested for research workers in the field of natural cell-mediated cytotoxicity (NCMC). Two recent articles are discussed which have been hailed as a fulfillment of these expectations. The first paper suggests that natural killer (NK) cells may have an antitumor effect in vivo. The second shows that interleukin-2, a factor which plays an important role in T-cell growth and function, also affects NK activity. Both papers (as well as commentary) present some problems of interpretation, especially the study on possible effects in vivo. Other studies are cited which indicate that thymus-deficient mice may be useful models for study of alternate pathways for development of cell-mediated cytotoxic mechanisms, of which NCMC may be the prime example. One commentator questions whether the function of NK cells need necessarily be the killing of tumor cells. The view is put forward that the two papers discussed (and 2 subsequent 'long' versions) support the view that during period of active growth of an area, publications of uneven quality are produced. (48 Refs)

83. STIMULATOR ACTIVITY OF PHA-LCM FOR NORMAL HUMAN HEMOPOIETIC PROGENITORS AND LEUKEMIC BLAST CELL PRECURSORS: SEPARATION BY ISOELECTRIC FOCUSING.

Fauser AA, Messner HA
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J Supramol Struct Cell Biochem; 15(1):41-48 1981

Factors in medium conditioned by leukocytes in the presence of phytohemagglutinin (PHA-LCM) that promote growth of human hemopoietic progenitors and leukemic blast cell precursors (LBC) were studied. PHA-LCM was prepared from peripheral blood of a patient with hemochromatosis. Growth-promoting factors in PHA-LCM were separated by isoelectric focusing. Nonadherent, mononuclear bone marrow cells from normal individuals and mononuclear, E-rosette-depleted peripheral blood cells from patients with acute myeloblastic leukemia were used as appropriate targets for the fractions. Factors promoting growth of pluripotent hemopoietic, erythroid, and granulocytic precursors had activity profiles of pH 5.0-6.5; these factors could be partially separated from a factor promoting LBC, which had a broader profile at pH 5.5-7.5, but not from each other. Isolation of growth-promoting factors with specificity for LBC would facilitate cloning of leukemic cells and permit study of the relationships between normal and leukemic hemopoiesis. (23 Refs)

84. PRODUCTS OF THE IMMUNE SYSTEM AS IMMUNOMODULATORS.

Sakiyama Y
Dept. Pediatrics, Hokkaido Univ. Sch. Medicine, Hokkaido, Japan
Nippon Rinsho; 39(4):156-162 1981

Research findings concerning the immunomodulating properties of transfer factor, thymus factors, lymphokines, and interferon were discussed. One particular property of transfer factor was imputing in vitro cytotoxic effects onto tumor cells. Of the thymus factors discussed (ie, thymosin, circulating thymic factor, thymic humoral factor, thymopoietin, and thymic epithelium supernatants), circulating thymic factor was found to have receptors observed in T-cells that were precultured with acute leukemia T-cell strains and normal human peripheral blood without the serum. Lymphokine activity has been observed in diseases exhibiting abnormal lymphocyte proliferation such as Hodgkin's disease, lymphoma, and myeloma, and antitumor activity of lymphokines was thought to be related to that of interferon. Antitumor effects of interferon have been observed in cases of osteosarcoma, lymphoma, melanoma, breast cancer, pharyngeal papilloma, and multiple myeloma. (20 Refs) (In JPN)

85. HUMAN TUMOR XENOGRAFTS IN ATHYMIC NUDE MICE AS A PRECLINICAL SCREEN FOR ANTICANCER AGENTS.

Ovejera AA, Houchens DP
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Semin Oncol; 8(4):386-393 1981

The role of the nude mouse-human tumor system in anticancer drug screening is discussed. Despite the possession of a small number of T cells, nude athymic mice are unable to reject skin grafts from widely divergent species. Successful xenotransplantation of human cancers to nude mice has provided an in vivo model for studying biologic characteristics of human tumors, especially response to therapy. Of the four most commonly studied tumor types, colorectal tumors and melanomas exhibit the highest rate of takes (greater than 60%), followed by lung tumors (approx 40-50%). Breast tumors are the most difficult to grow in nude mice: less than 20% of freshly implanted breast tumors are grown successfully. Breast (MX-1), colon (CX-1), and lung (LX-1) human tumor xenograft systems are included in the National Cancer Institute tumor panel. Chemotherapeutic responses of the three systems are described. The utility of human tumor xenografts for drug screening is discussed. (35 Refs)

86. PSYCHOSOMATIC ASPECTS OF CANCER.

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Dtsch Med Wochenschr; 106(47):1563-1565 1981

Theories concerning the influence of psychological and spiritual factors on the development and course of cancer are discussed. Classical psychosomatic diseases (eg bronchial asthma and peptic ulcer) are considered, and the interdependence of different factors in somatic-psychosomatic disease development is examined. Research into the relationship between psychological factors and the development of specific types of cancer is discussed with regard to the following aspects: risk behavior, such as alcohol or tobacco abuse; influence of significant life events, such as loss of a spouse; and identification of personality factors common to people with specific forms of cancer. Problems inherent in the design of and interpretation of results from such studies are noted. The influence of stress on tumor development in animals is considered, and stress related effects on humoral and cellular immunity in humans are described. It is concluded that the evidence to date supporting the theories concerning psychosomatic aspects of cancer is sparse. (14 Refs) (In GER)

87. INHIBITION OF H-Y CELL-MEDIATED CYTOLYSIS BY MONOCLONAL H-Y-SPECIFIC ANTIBODY.

Koo GC, Varano A
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Immunogenetics; 14(3/4):183-188 1981

Assays of H-Y-specific, cell-mediated cytolysis (CMC) in vitro were carried out with B6 female effector cells and B6 male target cells. Monoclonal H-Y antibody was added to the lytic assay to test whether the antigenic determinant(s) involved in H-Y-specific CMC was distinct from the serologically detected H-Y antigen. Significant blocking was observed, suggesting that the H-Y antigen detectable serologically is similar to H-Y antigen recognized by cytotoxic T cells. (Author abstract) (11 Refs)

88. SIGNIFICANCE OF CELLULAR PHARMACOKINETICS FOR THE CYTOTOXIC EFFECTS OF DAUNORUBICIN.

Andersson B, Beran M, Peterson C, Tribukait B
Dept. Medical Radiobiology, Karolinska Inst., Box 60204, S-104 01 Stockholm, Sweden
Cancer Res; 42(1):178-183 1982

The effect of free and DNA-linked daunorubicin on the colony-forming ability of granulocyte-macrophage committed stem cells and spleen colony-forming cells (ie, multipotent stem cells) from normal mice has been studied in vitro and in vivo. After incubation of bone marrow cells in short-term suspension cultures, both committed and multipotent stem cells were more sensitive to the free drug than to the DNA complex, whereas the reverse was found in vivo after iv injection. However, when the in vitro cell-killing effect was related to the cellular retention of daunorubicin, no difference in activity was found between free and DNA-linked drug. Incubation of the bone marrow cells with a higher drug concentration for a shorter time resulted in a considerably lower cell survival than incubation with a lower concentration for a longer time, the intracellular exposure dose being the same. When the in vivo cell survival was related to the cellular retention of daunorubicin, the DNA complex was slightly more toxic than free drug, which can be explained by the higher peak concentration obtained. The results obtained with committed granulocytic stem cells and multipotent stem cells were comparable. Thus, the observed discrepancy between the in vitro and in vivo toxicity of free and DNA-linked daunorubicin can be explained by the differences in cellular retention of daunorubicin under these two conditions; ie, the DNA complex probably acts as a slow-release preparation of daunorubicin. The results also demonstrated for the first time the importance of the peak concentration of daunorubicin in the target cells and indicate an important role of dose scheduling for the cytostatic effect of the drug. (Author abstract) (34 Refs)

89. POLYSACCHARIDE AND LIPOPOLYSACCHARIDE IMMUNOREGULATING MECHANISMS - USE OF PSK AS AN EXAMPLE.

Nomoto K
Cancer Res. Inst., Kyushu Univ., Kyushu, Japan
Nippon Rinsho; 39(4):110-115 1981

Characteristics of the mechanism and the effect of the polysaccharide Kureha (PSK) were investigated as an example of immunopotentiation by polysaccharides and lipopolysaccharides. Administration of PSK (50-100 mg/kg ip or 1,000 mg/kg po, continuously) to sarcoma 180 or Ehrlich tumor-bearing ICR mice resulted in disappearance of tumors after transient growth of the tumor. Antitumor effects were also observed for various homogenic strains of methylcholanthrene-induced tumors. Administration of PSK in mice with sarcoma 180 tumors increased splenocyte cytotoxicity. PSK had an inhibiting effect on macrophage aggregation in normal mice, but had stimulating effect on macrophage aggregation in tumor-bearing mice. Ip administration of PSK in cancer bearing mice resulted in recovery of delayed-type foot pad response to sheep RBC , and po administration resulted in a slightly lower degree of recovery. Ip administration of PSK in sarcoma 180 tumor-bearing mice with decreased production of interferon due to poly I:C stimulation resulted in a certain degree of recovery of interferon production. PSK was also observed to effect (1) fluctuations in preventing infections due to cancer, (2) changes in thymus function due to cancer, (3) inhibitory effects of cancerous ascites, (4) fractions of immune-inhibiting factors from cancerous abdominal ascites, and (5) mixes of accelerating factors and inhibiting factors in cancerous ascites and serum. (5 Refs) (In JPN)

90. EFFECTIVE MECHANISM OF CWSS BCG AND NOCARDIA RUBRA AS IMMUNOREGULATORS.

Ogura T, Yoshimoto T, Sakatani M, Nishikawa H, Masuno T, Kawase I, Namba M, Hirao F
Third Dept. Internal Medicine, Osaka Univ., Osaka, Japan
Nippon Rinsho; 39(4):94-102 1981

Basic immunopotentiating effects and mechanisms of antitumor effects and correspondences of BCG and Nocardia rubra (NR) were reviewed. Based on clinical studies showing the immunopotentiating effects of cell wall skeleton (CWS) on antitumorigenic macrophage activity, it was thought important to use CWS with chemotherapies, because chemotherapeutic agents have the potential to block immune function. Some animal studies have shown that BCG-CWS can reduce the incidence of chemically-induced cancer, but as human beings are different than rats and mice, the mechanism by which CWS has immunopotentiaing effects are still unclear. (40 Refs) (In JPN)

91. CORYNEBACTERIUM PARVUM STIMULATION OF ADHERENT AND NON-ADHERENT CYTOTOXIC CELLS IN MICE.

Hassan ZM, Rees RC, Potter CW
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Br J Cancer; 44(4):532-538 1981

Two naturally occurring cytotoxic cell populations have been identified in the peritoneal cavity of mice inoculated with C parvum (CP), and are distinguishable on the basis of target-cell reactivity and intrinsic properties. The first effector cell was non-adherent to nylon wool and glass and non-phagocytic. These cells were selectively cytotoxic to the NK-sensitive target cell line K562, and present in the peritoneal cavity of mice 2 days after treatment with 700 ug of CP. The second cytotoxic effector cell was adherent to nylon wool and glass, and killed EL4 lymphoma cells derived from in vivo tumor transplants; these target cells are susceptible to phagocytic cell killing, but not NK-cell cytotoxicity in short-term (4h) assays. The adherent cytotoxic population of effector cells was present 4 days after inoculation of CP. In vivo studies showed that CP injected ip induced resistance to ip challenge with lymphoma EL4 cells, but no resistance was evident when the challenge dose was administered sc. Adoptive-transfer studies showed that the effector cell type responsible for inhibiting tumor growth was nylon-wool adherent, probably CP-activated macrophages. (Author abstract) (26 Refs)

92. IMMUNOSUPPRESSIVE PROPERTIES AND CIRCULATING LIFE OF ACHROMOBACTER GLUTAMINASE-ASPARAGINASE COVALENTLY ATTACHED TO POLYETHYLENE GLYCOL IN MAN.

Abuchowski A, Davis FF, Davis S
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Cancer Treat Rep; 65(11/12):1077-1081 1981

The immunosuppressive effects and circulating life of Achromobacter glutaminase-asparaginase (GA) covalently attached to polyethylene glycol (PEG) were examined in human subjects following a single iv dose of 1,000 IU/m2. Plasma half-life of PEG-GA was 72 hr. Skin test reactivity to recall antigens (mumps and tuberculin) was lost in all four patients tested. In vitro phytohemagglutinin-induced blastogenesis, 'natural killing,' and phytohemagglutinin-induced cell cytotoxicity was diminished as long as enzyme levels were detectable. In vivo and in vitro activities returned to normal following total plasma clearance of enzyme. (Author abstract) (12 Refs)

93. IMMUNOPHARMACOLOGICAL EFFECTS OF IRRADIATION.

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Cancer Immunol Immunother; 11(4):239-242 1981

Effects of irradiation on immune response are reviewed. Localized irradiation has a depressive effect on T lymphocytes, monocytes, and null cells. Decreases in mitogen response, natural killer activity, and antibody- and phytohemagglutinin-induced cytotoxic response are produced. B lymphocyte response is apparently not affected, at least in the short term. Animal studies indicate a decrease in specific T cell cytotoxicity against tumor antigens, but the decrease has not been demonstrated in man. Preliminary results show that autologous rosette formation decreases after irradiation, indicating change in a nonsuppressor T cell population. Stress effects have been produced in animals at doses ranging from 0.12 to 16 gray local irradiation. Irradiation may combine with other agents to promote development of certain cancers. Some controversial studies suggest that irradiation itself may promote metastasis. The negative effects of irradiation may be reducible or avoidable by the use of other appropriate agents such as BCG. Clinical studies are required to determine the effects of irradiation on humans. (49 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

94. DESTRUCTION OF TUMOR CELLS BY MACROPHAGE PRECURSORS IN MOUSE AND MAN.

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Blut; 42(5):283-295 1981

Macrophage precursors exhibiting killer cell (K-cell) and natural killer cell (NK-cell) activity were detected in vivo in mice and humans. Peritoneal exudate was induced in C57/BL10 mice by ip injection of 100 ug Corynebacterium parvum. The exudate showed K-cell and NK-cell activity against Yac-1 and DBA/2 P815X tumor cells. Separation by column adherence produced a population of nonadherent cells, consisting of small lymphocytes and middle-sized, promonocyte-like cells (PML), which had K-cell and NK-cell activity. The PML lacked nonspecific esterase (a marker for mature macrophages), but when cultured produced mature macrophages after 3 days, indicating that the cultured cells were macrophage precursors. Similar cells were isolated from spleens of nu/nu mice and from human peripheral blood. The activity of these cells was absorbed by allogeneic antimacrophage serum Mph 1.2 with rabbit complement. The cells were nonadherent and nonphagocytic. Results indicate that macrophage precursor cells, as well as mature macrophages, are released from bone marrow into peripheral circulation in mice and humans, and that these precursor cells have cytotoxic effects on tumor cells. (24 Refs) (In GER)

95. EXPERIMENTAL AND CLINICAL STUDIES OF IMMUNOLOGICAL ACTIVITY OF MONOCYTES IN TUMOR-BEARING HOSTS. I. KINETICS OF PERITONEAL MACROPHAGE FUNCTIONS IN TUMOR-BEARING MICE.

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Dept. Surgery, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi, Hiroshima 734, Japan
Hiroshima Daigaku Igaku Zasshi; 29(3):491-502 1981

The immunological reactivity of nonactivated and Corynebacterium parvum (C parvum)-activated peritoneal macrophages in tumor-bearing mice was investigated in relation to several macrophage functions - chemotaxis, phagocytosis, cytostasis, cytolysis and serum lysozyme activity. Peritoneal exudate cells (PEC) decreased from Day 14 after tumor inoculation and more significantly at day 28. The number of PEC from tumor-bearing mice treated with C parvum increased, but, in the late stage, less than in normal C parvum-treated mice. The response to WBC-derived chemotactic factor was significantly depressed in the early stage of the tumor-bearing mice and did not recover until the late stage. It was increased by injection of C parvum, but less after Day 7 than that of C parvum-treated normal mice. Phagocytosis of latex beads increased significantly within 10 days after tumor inoculation, then progressively decreased to normal and remained normal until death. It was increased by C parvum as much as that from C parvum-treated normal mice. Cytostatic activity of tumor-bearing mice increased in the early stage, then decreased. It seemed to be related to immunocompetence and prognosis of tumor-bearing mice. C parvum increased the even activity in the late stage. Cytolytic activity of tumor-bearing mice was initially absent, but b ecame apparent when the tumor grew, reached a max on Day 10 and decreased in the late stage. It was enhanced by C parvum, but less in tumor-bearing mice than in normal mice. Serum lysozyme activity, a possible marker of macrophage function, showed a small increase in tumor-bearing mice but no further progression. It either increased or decreased after treatment with C parvum. (Author abstract) (39 Refs) (In JPN)

96. EXPERIMENTAL AND CLINICAL STUDIES OF IMMUNOLOGICAL ACTIVITY OF MONOCYTES IN TUMOR-BEARING HOSTS. II. CYTOSTATIC ACTIVITY OF TUMOR-BEARING MOUSE PERITONEAL MACROPHAGES FRACTIONATED BY VELOCITY SEDIMENTATION.

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Hiroshima Daigaku Igaku Zasshi; 29(3):503-517 1981

The cytostatic activity of nonactivated and Corynebacterium parvum (C parvum) activated peritoneal macrophages from tumor-bearing mice was reported previously. In the present study, macrophages were fractionated by velocity sedimentation and analyzed to investigate the immunocompetence of tumor-bearing mice. Cytostatic activity of macrophages from normal mice was absent at low effector to tumor (E/T) ratios but present at high E/T ratios. On the other hand, macrophages from tumor-bearing mice showed some cytostatic activity at low E/T ratios. The difference in cytostatic activity between normal and tumor-bearing mice seemed partially dependent on the E/T ratio. It was suggested that cytostatic activity of unfractionated macrophages be tested at many E/T ratios. According to cell size by velocity sedimentation, the sedimentation profile of peritoneal exudate cells (PEC) of normal mice showed a bimodal distribution. In contrast, that of C parvum-treated normal mice showed a unimodal distribution. The sedimentation profile of the PEC from tumor-bearing mice was unimodal in the early stage and bimodal in the late stage. That of PEC from C parvum-treated tumor-bearing mice showed no clear unimodal distribution. Cytostatic activity of macrophages from normal mice increased with cell size and was max with the largest macrophages. On the other hand, cytostatic activity of fractions containing small and medium-sized macrophages from tumor-bearing mice was high in the early stage and significantly lower in the late stage. However, cytostatic activity of fractions containing large macrophages from tumor-bearing mice was as high as that from normal mice. These results suggest that the cytostatic activity of fractionated macrophages could be a good indicator for analyzing macrophage-mediated host resistance to tumors. (Author abstract) (20 Refs) (In JPN)

97. EXPERIMENTAL AND CLINICAL STUDIES OF IMMUNOLOGICAL ACTIVITY OF MONOCYTES IN TUMOR-BEARING HOSTS. III. MONOCYTE FUNCTIONS OF PATIENTS WITH GASTRIC CANCER.

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Hiroshima Daigaku Igaku Zasshi; 29(3):519-526 1981

Monocyte functions were investigated by examining chemotaxis, serum lysozyme activity, cytostasis and cytolysis in patients with gastric cancer. The chemotactic response of patients with gastric cancer was lower than that of the healthy controls. However, the reduction was not closely related to the clinical stage. Lysozyme levels in patients with gastric cancer were higher than those of the healthy controls. In Stage I, a significant elevation was observed in lysozyme levels, but in Stages II, III, and IV, the levels were not different from those of the control group. There was no cytolytic activity in patients with gastric cancer or in the healthy controls at an effector to tumor (E/T) ratio of 100:1. Cytostatic activity of patients with gastric cancer was higher than that of the healthy controls at an E/T ratio of 100:1. It is concluded that cytostatic activity of fractionated monocytes may be a useful indicator for analyzing macrophage-mediated host resistance to tumors. (Author abstract) (44 Refs) (In JPN)

98. EFFECTS OF LIPOSOME STRUCTURE AND LIPID COMPOSITION ON THE ACTIVATION OF THE TUMORICIDAL PROPERTIES OF MACROPHAGES BY LIPOSOMES CONTAINING MURAMYL DIPEPTIDE.

Schroit AJ, Fidler IJ
Cancer Metastasis and Treament Lab., Natl. Cancer Inst. Frederick Res. Center, Frederick, MD, 21701
Cancer Res; 42(1):161-167 1982

Various vesicle structures and lipid compositions have been studied to identify the optimal type of liposome for delivery of the macrophage-activating agent muramyl dipeptide (MDP) to macrophages. Evaluation of the ability of liposomes to be phagocytosed by macrophages established that optimal initial rates of engulfment were obtained when multilamellar vesicles (MCV) composed of distearoylphosphatidylcholine (18:0 PC): phosphatidylserine (PS) (7:3 mol ratio) were used. MLV composed exclusively of 18:0 PC were phagocytosed at rates greater than or equal to those of MLV composed of egg phosphatidylcholine (PC):PS, whereas MLV composed only of egg PC were very poorly phagocytosed. Although phagocytosis was enhanced by incorporation of PS into MLV, the inclusion of PS brought about significant enhancement in liposome permeability in the presence of serum. The inclusion of PS, however, was a requirement for the delivery of MLV to the lungs following iv injection into mice whether used in conjunction with 18:0 PC or egg PC. Activation of macrophages to become tumoricidal against syngeneic tumor cells with liposome-encapsulated MDP was superior in both degree and duration when MLV composed of 18:0 PC:PS (7:3 mol ratio) were used. MLV were found to be superior to large unilamellar vesicles containing equal amounts of lipid and entrapped MDP. On the other hand, higher levels of macrophage activation were obtained when an equivalent amount of a lipophilic MDP derivative, muramyl tripeptide:phosphatidylethanolamine, was incorporated into the liposome bilayer irrespective of whether the adjuvant was incorporated in liposomes composed of 18:0 PC:PS or egg PC:PS. (Author abstract) (42 Refs)

99. RELEASE OF ERYTHROPOIETIN FROM MACROPHAGES BY TREATMENT WITH SILICA.

Rich IN, Anselstetter V, Heit W, Zanjani E, Kubanel B
Dept. Transfusion Medicine, Univ. Ulm, Ulm, W. Germany
J Supramol Struct Cell Biochem; 15(2):169-176 1981

Stimulation of murine macrophage-containing cell suspensions to produce an erythropoietic stimulating factor (ESF) by silicon dioxide (silica) was studied. Cell suspensions were prepared from the spleens of C57Bl mice. Samples consisting of 8 x 10(6) cells were incubated with 10(-4) gm silica/ml. ESF activity was measured in Swiss Webster mice using the polycythemic mouse (PCM) bioassay. Injection of 0.4, 0.8, or 1.6 ml of supernatant from silica-treated cell suspensions ip into PCM produced RBC 59Fe incorporation of 2.06%, 4.14%, and 10.43%, respectively. The activity of ESF was almost completely abolished by antiserum against erythropoietin (Ep). Erythropoietic response to Ep and purified samples of ESF were parallel. The presence of 1% fetal calf serum (FCS) in cell suspensions enhanced the effect of ESF compared to that produced in the absence of FCS. Incubation of cells with 2 mM Ca++ produced the same enhancement of ESF effect as FCS treatment. Results indicate that ESF is Ep and suggest for macrophages an important role in erythropoiesis. (19 Refs)

100. METABOLISM OF EXOGENOUS ARACHIDONIC ACID BY MURINE MACROPHAGE-LIKE TUMOR CELL LINES.

Stenson WF, Nickells MW, Atkinson JP
Div. Gastroenterology, Jewish Hosp. St. Louis, St. Louis, MO, 63110
Prostaglandins; 21(5):675-689 1981

Murine macrophage-like cell lines, J774.2, P388D1, RAW264.7 and PU-5-1R, were incubated with exogenous arachidonic acid (AA). The major metabolites were identified by comigration with known standards in TLC and HPLC and by characteristic behavior following reduction. During a 30 min incubation J774.2 cells metabolized exogenous 14C-AA (10 uM) to PGE2 (14.8%), 12-hydroxy-5,8,10-heptadecatrienoic acid (HTT) (13.0%), thromboxane B2 (TXB2) (7.4%), PGD2 (4.4%) and PGF2alpha (3.0%). The remainder was incorporated into phospholipids (39.0%), triglycerides (6.1%), and as yet unidentified metabolites (8.2%). No PGF1alpha was found. Metabolism of exogenous AA was rapid, being greater than 90% completed at 3.5 min. Metabolism of exogenous AA is not increased by the simultaneous addition of macrophage stimuli including the cation ionophore A-23187, particulate phagocytic stimuli and endotoxin. The synthesis of cyclooxygenase products was inhibited by low doses of indomethacin (ID50 = 0.6 uM) while the synthesis of TXB2 and HHT was selectively inhibited by benzylimidazole (ID50 = 9.5 uM). Identification of a probable lipoxygenase product is being pursued. The synthesis of this product is not inhibited by indomethacin and migrates with an Rf value close to 5,12-diHETE in TLC. P388D1 and RAW264.7 cells metabolize exogenous AA to the same products as J774.2, but in different proportions, while PU-5-1R does not produce cyclooxygenase metabolites to any appreciable extent. (Author abstract) (22 Refs)

101. DECREASED ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY IN VARIOUS TYPES OF LEUKEMIA IN MAN.

Jakobisiak M, Janowska-Wieczorek A, Dobaczewska H, Kantoch M, Marczak M, Oblakowski P, Lasek W, Sosnowska M
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Scand J Haematol; 27(3):181-185 1981

Antibody-dependent cellular cytotoxicity (ADCC) by cells from peripheral blood was studied in patients with: chronic lymphocytic leukemia (CLL), chronic granulocyte leukemia (CGL), acute lymphoblastic leukemia, acute non-lymphoid leukemia (ANLL) and compared with that of healthy donors. The ADCC activity in all the types of leukemia was on the average lower as compared with the control values, being especially low in both CLL and CGL. Further, it has also been shown that the ADCC activity of non-leukemic blood cells in ANLL was lower as compared with control values. The latter observation indicates that, at least in ANLL, the reduced ADCC potential of peripheral blood cells is not due to dilution of effector cells by poorly- or non-active leukemic cells. (Author abstract) (23 Refs)

102. COMPARISON OF MONOCYTE AND ALVEOLAR MACROPHAGE ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY AND FC-RECEPTOR ACTIVITY.

Garagiola DM, Huard TK, LoBuglio AF
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Cell Immunol; 64(2):359-370 1981

The cytotoxic potential of rabbit peripheral blood monocytes and alveolar macrophages in antibody-dependent cellular cytotoxicity (ADCC) toward both RBC (RBCox) and tumor cell (CEM T-lymphoblast) targets was examined. ADCC was measured in a 4-hr 51Cr-release assay. Alveolar macrophages were more efficient at killing the tumor cell targets (optimally sensitized with rabbit antisera) than monocytes at similar effector cell/target cell (E/T) ratios. Tumor cell targets sensitized with with seven different antisera (anti-CEM) were lysed by alveolar macrophages but not by the monocytes. In marked contrast the monocytes were more effective at lysing the sensitized RBC target cells. The degree of cytolysis of RBCox and CEM was dependent on the E/T ratio and the degree of sensitization of these target cells. It was demonstrated that the effector cell selectivity in ADCC was directly related to their ability or inability to bind the sensitized target cells as determined by Fc-receptor rosette formation. The transition from monocyte to macrophage may, therefore, have resulted in an alteration in the criteria necessary for Fc-receptor binding to antibody-sensitized target cells and subsequent ADCC. (Author abstract) (40 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

103. A MONOCLONAL ANTIBODY SPECIFIC FOR IMMATURE HUMAN HEMOPOIETIC CELLS AND T LINEAGE CELLS.

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J Immunol; 127(6):2269-2274 1981

An anti-human monoclonal antibody (RFB-1) has been produced that reacts with a group of hemopoietic precursor cells in human bone marrow. These include terminal deoxynucleotidyl transferase-positive (TdT+) cells and myeloid colony-forming unit cells, functionally identifiable progenitor cells of the granulocytic-monocytic series. The expression of RFB-1 antigen on myeloid cells decreases as the cells become more mature; myeloblasts are weakly RFB-1+ but most promyelocytes are RFB-1-. RFB-1 also reacts with TdT+ thymic blast cells and cortical thymocytes but is unreactive with TdT- medullary thymocytes, although the majority of peripheral T cells are weakly RFB-1+. RFB-1 is the first anti-precursor cell reagent that labels human TdT+ cells in both the thymus and bone marrow as well as hemopoietic precursor cells but is unreactive with pre-B blasts and B lymphocytes. (Author abstract) (37 Refs)

104. MONOCLONAL ANTIBODIES REACTIVE WITH ACUTE MYELOGENOUS LEUKEMIA CELLS.

Linker-Israeli M, Billing RJ, Foon KA, Terasaki PI
1000 Veteran Ave., Room 15-22, Los Angeles, CA, 90024
J Immunol; 127(6):2473-2477 1981

Two cytotoxic monoclonal antibodies (D5D6 and C10H5) were raised to acute myelogenous leukemia (AML) cells. One of them, D5D6, reacted with 100% of the cells from 44/50 AML patients. The second, C10H5, reacted with 100% of the cells from 13/39 AML patients. D5D6 and C10H5 were cytotoxic to 100% of the monocytes from all healthy donors tested. Apart from monocytes, these antibodies did not react with any other peripheral blood cells from normal donors or with cancerous cells either from cell culture lines or from patients with chronic myelogenous leukemia (CML), lymphoid leukemias, or solid tumors. These antibodies inhibited the growth of the myeloid-monocytic stem cell, the CFU-C, and reacted with a minor population of normal bone marrow cells by immunofluorescence. Both D5D6 and CH5 have potential utility for the differential diagnosis of acute leukemia, for the detection of early leukemic relapse, and for enrichment of human stem cells. (Author abstract) (18 Refs)

105. PHENOTYPES OF HUMAN NATURAL KILLER CELL POPULATIONS DETECTED WITH MONOCLONAL ANTIBODIES.

Zarling JM, Clouse KA, Biddison WE, Kung PC
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J Immunol; 127(6):2575-2580 1981

In our recent studies, human natural killer (NK) cell activity was found to be decreased two- to four-fold after treatment of monocyte-depleted peripheral mononuclear cells with monoclonal antibody OKM1 and complement (C). The present study was undertaken to determine whether there is an additional population of NK cells that is OKM1-, since treatment with OKM1 and C decreased, but did not eradicate, NK cell activity. Treatment of lymphocytes with monoclonal antibody OKT11A, which reacts with all sheep red blood cell rosetting lymphocytes, and C also decreased NK cell activity. Although approximately 90% of OKT11A+ cells are OKT3+, NK cell activity resides within the OKT11A+ cell population, which is OKT3-since OKT3-cell depletion fails to decrease NK cell activity. Double fluorescence analysis of OKT3-depleted lymphocytes revealed that 54% of the OKM1+ cells are OKT11A- and 45% of the OKT11A+ cells are OKM1-, thus demonstrating that within the OKT3-depleted population, approximately one-half the OKM1+ cells are OKT11A- and vice versa. Treatment of lymphocytes with OKM1 together with OKT11A and C decreased NK cell activity against three NK-sensitive leukemia lines-K562, MOLT-4, and HSB-2 more than did treatment with either antibody alone; virtually no lytic activity was retained after elimination of OKM1+ and OKT11A+ cells. The results thus provide strong evidence that there are at least two populations of human NK cells; one is OKM1+ and the other is OKT11A+. (Author abstract) (19 Refs)

106. ANTI-K562 CELL MONOCLONAL ANTIBODIES RECOGNIZE HEMATOPOIETIC PROGENITORS.

Young NS, Hwang-Chen SP
Clinical Hematology Branch, Natl. Heart, Lung, and Blood Inst., NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 78(11,part2):7073-7077 1981

The K562 leukemia cell has properties of self-renewal and pluripotency similar to those of the hematopoietic stem cell. Monoclonal antibodies to K562 cells have been produced by using hybridoma technology. By radioimmunoassay, some anti-K562 cell antibodies also bind to RBC antigens or peripheral blood mononuclear cells; others are more specific for K562 cells. Antibody binding to hematopoietic progenitors was assayed by using the ability of these cells to form colonies in vitro. After exposure of human bone marrow cells to anti-K562 antibodies and complement, myeloid or erythroid colony formation was inhibited. Some of the inhibitory antibodies showed little binding to mature blood cells by radioimmunoassay, immunofluorescence, and complement cytotoxicity, suggesting that they recognize antigens specific to undifferentiated cells. With the fluorescence-activated cell sorter, one inhibitory antibody was shown to sta in only 3% of bone marrow cells. Inhibitory anti-K562 antibodies also bind to myelogenous leukemia cells and virus-transformed lymphocytes. Thus, these antibodies appear to recognize antigens shared by normal hematopoietic progenitors, leukemic cells, and transformed lymphocytes. (Author abstract) (26 Refs)

107. TRANSLATION OF LYMPHOCYTE MRNA INTO BIOLOGICALLY-ACTIVE INTERLEUKIN 2 IN OOCYTES.

Bleackley RC, Caplan B, Havele C, Ritzel G, Mosmann TR, Farrar JJ, Paetkau V
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J Immunol; 127(6):2432-2435 1981

A variant line of murine T lymphoma EL4 produces high levels of the lymphokine Interleukin 2 (IL 2) when it is stimulated with phorbol myristate acetate. We have extracted poly A+ RNA from the stimulated cells and injected it into Xenopus laevis oocytes. The injected oocytes synthesize a material with biological and biochemical properties of murine IL 2. Namely, it stimulates the continued growth factor of a cloned, cytotoxic T-cell line (the T-cell growth factor assay) and it chromatographs on a gel filtration column (G-100) with IL 2 produced by the stimulated EL4 line. The RNA responsible for the biologic activity sediments with markers of 11 to 12S in a sucrose gradient. The IL 2 produced by injected oocytes from a given preparation of mRNA is about 1% of the amount produced by the EL4 cells stimulated originally with phorbol myristate acetate. When RNA is extracted and purified from unstimulated EL4 cells it does not induced IL 2 production in oocytes. We conclude that IL 2 is essentially protein in nature, that the protein is coded for by poly A+ mRNA, and that the amount of this mRNA increases significantly after stimulation of the variant EL4 cells with the inducer phorbol myristate acetate. (Author abstract) (19 Refs)

108. GROWTH OF NORMAL AND TUMOUR HAEMOPOIETIC CELLS OF GLASS COVERSLIPS IN PERITONEAL CAVITY OF MICE: II. IMMUNOLOGICAL IDENTIFICATION OF BONE MARROW COLONY-FORMING CELLS.

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Folia Biol (Praha); 27(4):255-264 1981

Erythroid (CFU-E) and granulocyte/macrophage (CFU-GM) colonies grown on glass coverslips (GC) inserted into the peritoneum of mice were identified by immunologic tests. GC were inserted into the peritoneal cavities of AKR, C57BL/6, and (CBA x C57BL/6)F1 (CBF1) mice. Hemopoietic colonies were grown on the GC by injection of normal CBF1 bone marrow cells (BMC), K-2 erythroleukemia cells, or RAL Rauscher leukemia cells. Colonies were characterized by reaction with rabbit anti-mouse-brain serum (RAMBS) and antibodies to Ab-Eb, an antigen found on all erythroid cells, but not on mature erythrocytes. RAMBS or anti-Ag-Eb with complement had no effect on the colony-forming capacity of BMC. RAMBS inactivated 44% of cells forming colonies in the spleen (CFU-S). Anti-Ag-Eb reduced immature erythroid cells in BMC samples to 75% of control values. Results indicate that CFU-E and CFU-GM cells represent committed hemopoietic progenitors, since they contain little or no Ag-Eb antigen. (26 Refs)

109. BONE MARROW TRANSPLANTS: FROM REMISSION TO CURE?.

Meo C
No affiliation given
MMW; 123(42):1555-1557 1981

The development and success of the use of bone marrow transplantation (BMT) in the treatment of adults with acute leukemia is reviewed. Initial use of this technique in patients with therapy-resistant leukemia is described, and later use of BMT as an alternative therapy in patients in early stages of the disease is noted. The BMT procedure is discussed with regard to patient characteristics that improve the chances of successful treatment, morbidity and length of hospitalization of the patients, incidence of relapses, and the occurrence of transplant rejection. In addition, the technique is examined with regard to two major problems: the need for an HLA-identical sibling and the occurrence of graft-versus-host-disease (GVHD). Recent attempts to surmount these problems are described. The potential use of monoclonal antibodies against selected human T-cells in prevention or treatment of GVHD is noted. It is suggested that the success of BMT as an alternative treatment for adults with acute leukemia is reflected in the marked increase in the number of patients treated with this procedure in the past 5 yr. An interview with E.D. Thomas is presented; specific aspects of BMT therapy are discussed. (no Refs) (In GER)

110. HUMAN AUTOLOGOUS ROSETTES. II. FURTHER CHARACTERIZATION: MARKERS AND FUNCTIONS.

Rucheton M, Caraux J, Rey A, Thierry C, Esteve C, Valles H, Dufer J, Desplaces A, Zagury D, Serrou B

Laboratoire d'Immunopharmacologie des Tumeurs, INSERM U 236, ERA-CNRS No., ERA-CNRS No 844, Centre Paul Lamarque, Hopital St. Eloi, B.P. 5054, 34033 Montepellier Cedex, France

Cell Immunol; 64(2):312-323 1981

Purification of peripheral blood lymphocytes able to form autologous rosettes (ARFC) overnight has been obtained with satisfactory yield and enrichment, using short-term centrifugation on a Percoll cushion. Purified ARFC form E-rosettes, express human T-lymphocyte antigens, and contain cell-bearing Fc receptors for IgM but very few for IgG. They are also OKT4 positive. Morphological structure and cytochemistry (beta-glucuronidase and acid phosphatase) do not suggest activation. The ARFC subset has poor antibody-dependent cell-mediated cytotoxicity and NK activity. They respond strongly to PHA and demonstrate a higher response in mixed allogeneic or autologous culture compared to non-ARFC or total PBL. (Author abstract) (42 Refs)

111. H-2 ANTIGEN EXPRESSION ON TERATOCARCINOMA CELLS PASSAGED IN GENETICALLY RESISTANT MICE IS REGULATED BY LYMPHOID CELLS.

Ostrand-Rosenberg S, Cohn A

Dept. Biological Sciences, Univ. Maryland Baltimore County, Catonsville, MD, 21228

Proc Natl Acad Sci USA; 78(11,part2):7106-7110 1981

Previous studies have demonstrated that resistance and susceptibility to the 402AX testicular teratocarcinoma are under genetic control in the mouse. Under normal culture conditions or when passaged in genetically susceptible hosts, the nullipotent 402AX cells do not express H-2 antigens. However, when passaged in genetically resistant animals, the tumor cells become strongly positive for H-2 antigens in the absence of other indications of differentiation. These studies suggested that H-2 antigen modulation on teratocarcinoma cells is mandatory for an effective host cell-mediated immune response against this tumor. The present studies further examine the role of H-2 antigen modulation on teratocarcinoma cells and determine which host cell populations are mediating H-2 modulation on the tumor cells. Reconstitution of lethally irradiated susceptible hosts with resistant bone marrow extends the mean survival time of the host but does not confer complete resistance. Teratocarcinoma cells passaged in such reconstituted hosts do not express H-2 antigens. Two lines of evidence suggest that H-2 antigen modulation is mediated by lymphoid cells; (i) sublethal irradiation of genetically resistant hosts inhibits H-2 antigen modulation on teratocarcinoma cells passaged in vivo and (ii) immunological priming can overcome the loss of H-2 modulation that is normally associated with aging in genetically resistant hosts. Genetically susceptible mice can be fully reconstituted for tumor rejection and H-2 antigen expression on teratocarcinoma cells by reconstitution with genetically resistant bone marrow plus lymphoid cells from tumor-primed resistant hosts. These results: (i) imply the necessity for H-2 antigens on tumor cells for an effective host cell-mediated immune response against the tumor, and (ii) indicate that host lymphoid cells regulate H-2 antigen expression on tumor cells passaged in vivo. (Author abstract) (18 Refs)

112. CELL VOLUMES OF NORMAL AND MALIGNANT MONONUCLEAR CELLS.

Chapman EH, Kurec AS, Davey FR

(c/o Davey) Div. Clinical Pathology, State Univ. New York, Upstate Medical Center, 750 East Adams St., Syracuse, NY, 13210

J Clin Pathol; 34(10):1083-1090 1981

The cell vol of mononuclear cells, T lymphocytes, B lymphocytes, and monocytes from the peripheral blood of 20 normal individuals were compared to neoplastic lymphoid cells from 14 patients with chronic lymphocytic leukemia (CLL), 20 individuals with acute lymphocytic leukemia (ALL), and 18 cases of non-Hodgkin's lymphoma (NHL). Normal T cells were obtained by rosetting mononuclear cells with sheep RBC followed by centrifugation on a gradient composed of Ficoll and diatrizoate salts. Monocyte populations were prepared by adhering mononuclear cells to plastic dishes and B cells were obtained by the depletion of T lymphocytes and monocytes from a mononuclear cell population. Cell vol were determine on a Coulter Counter Model H4 Channelyzer. In normals, the av mean cell vol (MCV) of T lymphocytes was smaller than B lymphocytes and the av MCV of B lymphocytes was smaller than the av MCV of monocytes (p less than 0.05). The av MCV of lymphocytes from patients with CLL was smaller than the av MCV of normal B cells (p less than 0.01). The av MCB of lymphoblasts from cases of ALL was larger than the av MCV of normal peripheral blood lymphocytes (p less than 0.01), in addition, the size of lymphoblasts showed great variation within and among cases of ALL. The MCV of lymphocytes from most cases of NHL was larger than the MCV of lymphocytes from reactive lymph nodes and from the peripheral blood of normal individuals. An association was observed between the MCV of neoplastic cells and the classification according to Rappaport. We believe that the measurement of lymphoid cell vol may be helpful in the diagnosis and prognosis of patients with a variety of lymphoproliferative disorders. (Author abstract) (40 Refs)

113. AUER BODIES IN ACUTE LYMPHOCYTIC LEUKAEMIA AND B-CELL LYMPHOMA: EVIDENCE FOR A COMMON PROGENITOR OF MYELOID AND LYMPHOID CELLS.

Jehn U, Thiel E

Medizinische Klinik III, Klinikum Grosshadern, Ludwig-Maxmilians-Universitat Munchen, Marchioninistrasse 15, D-8000 Munich 70, W. Germany

Blut; 43(1):7-14 1981

Two patients (16-yr old male and 56-yr-old female) with hemopoietic malignancies, each having two distinct cell populations with lymphoblastic and myeloblastic characteristics are described. Most of the immature cells in each had a typical lymphoid phenotypes, but in a few blasts, Auer bodies were found. Evidence for the existence of a common stem cells for both myeloid and lymphoid cells displaying a highly significant morphological marker in combination with immunological phenotyping is presented. In the patient with acute lymphocytic leukemia (ALL), 70% of the blasts displayed T-cell markers while 1/3 remained unidentified. Only 42% of lymphoid cells in the B-cell lymphoma patient could be characterized as monoclonal B cells. In both cases there was a minor (5-10%) population of blasts displaying azurophilic cytoplasmic granules and staining for peroxidase, atypical for lymphoblasts. Auer bodies were found in 3-5% of immature cells. The results indicated that both disorders should be reclassified as lymphoproliferative diseases with mixed leukemic cell populations, one with a predominance of pre-T-ALL phenotype and the other of the B-cell type. (25 Refs)

114. SPECIFIC REVERSAL OF CYTOLYTIC T LYMPHOCYTE-TARGET CELL INTERACTION.

Balk SP, Mescher MF
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Supramol Struct Cell Biochem; 16(1):43-52 1981

An assay of the reversal of specific cytolytic T cell (CTL)-target binding is described. Spleen cells from C57BL/6 B6 H-2b mice were immunized with P815 (H2d) mastocytoma cells to produce responder cells against the H-2d major histocompatibility complex (MHC). (BALB/c x DBA/2) F1 (CD2, H-2d) mice were immunized with EL4 (H2b) thymoma cells to produce responder cells against the H-2b MHC. CTL were produced by stimulating primed spleen cells with irradiated allogeneic spleen cells. CTL-target cell conjugate were formed by mixing CTL and 51Cr-labeled target cells. Lysis of the target cells, which occurs rapidly at 37 C was prevented by incubation at 23 C. Reversal of conjugate formation was measured at various times by adding Ca++ and raising the temperature to 37 C, allowing lysis and consequent release of 51Cr. CTL-labeled P815 conjugate were stable in suspension, but were reversed by addition of unlabeled P815 cells. CTL-spleen cell and CTL-tumor cell conjugates could be reversed only by cells of the same H-2 type. Tumor cells produced greater specific reversal of conjugation than spleen cells, indicating that tumor cells were more tightly bound than spleen cells. Reversal evidently involves release of one target cell and binding of another. (16 Refs)

CMI METHODOLOGY

115. PREPARATION OF STABLE TARGET CELLS FOR ANTI-HERPES SIMPLEX VIRUS CYTOTOXIC T LYMPHOCYTES.

Sonoda S, Hitsumoto Y, Utsumi S, Takami S, Oseto M, Minamishima Y
Ehime Prefectural Inst. Public Health, Sanban-cho, Matsuyama, Ehime 790, Japan
Microbiol Immunol; 25(10):999-1010 1981

With the use of SKa, an avirulent strain of herpes simplex virus (HSV), and a methylcholanthrene-induced mouse sarcoma cell line (Meth A cells), a reliable target cell system was developed for detection of cell-mediated cytotoxicity directed against HSV-infected cells. Also discussed are the assessment of improved measurement for HSV-specific cytotoxic T lymphocytes (CTL) generated in BALB/c mice, and the practical value of avirulent HSV for the study of cell-mediated immunity against HSV. SKa propagated in Vero cells did not replicate in Meth A cells when infected at multiplicity of infection (moi) 3, whereas strain KOS at the same moi replicated in these cells as well as in Vero cells. Generation of HSV-antigen by SKa advanced so slowly that it reached the max level at 18 hr post-infection (pi) while KOS infection resulted in a rapid production of HSV antigens which was accomplished within 6 hr pi and followed by abrupt response of cytolysis. SKa-infected Meth A cells released no more 51Cr than noninfected control cells, whereas KOS-infected cells induced an abrupt increase in 51Cr-release at around 8 hr pi. SKa-infected Meth A targets were specifically lysed by immune spleen cells stimulated with HSV-infected Meth A antigens, but not by spleen cells treated with noninfected Meth A cells alone. Thy-1 antigen positive cells are responsible for HSV-specific cytotoxicity. The system described should be valuable in studies of cell-mediated cytotoxicity directed against HSV-infected cells. (42 Refs)

116. RED BLOOD CELLS COATED WITH TUMOR CELL EXTRACTS AS TARGETS IN 51CR RELEASE ASSAYS.

Karjalainen HE, Mantyjarvi RA
Dept. Clinical Microbiology, Univ. Kuopio, POB 138, SF-70101 Kuopio 10, Finland
Acta Pathol Microbiol Scand [C]; 89(4):315-319 1981

Sheep RBC were coated with tumor cell antigens prepared by extractions with 3M KCl. The coated cells were labelled with 51Cr and used as targets in immuno-assays. The technique was found suitable for complement-mediated as well as antibody-dependent cell-mediated reactions, and it offers several applications for use in tumor immunology. (Author abstract) (35 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abuchowski A 92
Adelsberg BR 1
Aizawa S 47
Alferov AN 19
Andersson B 88
Angyal I 37
Anselstetter V 99
Aoyama H 46
Armstrong D 1
Asamoto H 28
Atfield G 57
Atkinson JP 100
Axberg I 26
Baird SM 48
Balcerzak SP 66
Baldwin RW 44
Balk SP 114
Bannasch P 56
Barlozzari T 42
Beattie GM 48
Beran M 88
Biddison WE 105
Billing RJ 104
Bleackley RC 107
Bockman RS 72
Bodger MP 103
Boquist L 50
Boyce JT 51
Boyer C 80
Brautigam W 86
Brettman L 3
Britt J 11
Brooks CG 43
Brooks CG 44
Brown AE 1
Bubbers JE 54
Bur M 21
Burakoff SJ 74
Burchardt K 25
Calabro F 16
Cannon GB 14
Caplan B 107
Caraux J 110
Carlsson SR 50
Catovsky D 6
Cawley JC 18
Cesarini C 42
Chandler JP 53
Chapman EH 112
Charubala R 15
Cherchi M 6
Christoffersen 41
Clark EA 61
Clausen PP 41
Clouse KA 105
Cohn A 111
Colombo MP 58
Connor R 14
Crawford DH 20
Csecsi-Nagy M 37
Cunningham-Rund 1
Cunningham-Rund 1
Cunningham-Rund 3
Dadonna PE 73
Dang AQ 15
Davey FR 112
Davis FF 92
Davis S 92
Dean JH 14
Delia D 103
Deodhar SD 49
Desplaces A 110
Distasio JA 68
Dobaczewska H 101
Doetsch PW 15
Domingue GJ 52
Dorf ME 79
Dufer J 110
Durack DT 2
Durden DL 68
Ebina Y 46
Edwards A 23
Edwards JM 20
El'chits TV 19
Elgert KD 62
Elmubarak AK 55
Enders B 21
Engel D 61
Engers HD 60
Ershler WB 11
Esteve C 110
Fabianova J 7
Falus A 37
Fan PT 4
Fanger MW 18
Farrar JJ 107
Farrar WL 62
Fauser AA 83
Fekete B 37
Festenstein H 57
Fidler IJ 98
Fixa B 36
Flannery GR 43
Flick MB 15
Flynn B 11
Foo AS 62
Foon KA 104
Fougereau M 80
Fox RM 69
Francis GE 103
Fridliand DIu 35
Fuchimoto S 32
Fudenberg HH 45
Fujita Y 30
Furuta M 28
Fust G 37
Garagiola DM 102
Gautam S 49
Gautam SC 49
Gewurz H 65
Gidlund M 76
Gillis S 81
Giuliano AE 24
Gnagy MJ 45
Gold J 1
Golub SH 24
Gomez R 6
Gottlieb MS 4
Govallo VI 9
Granger SM 103
Gray JD 44
Greene JB 3
Greene MI 78
Gresser I 76
Grinevich IuA 19
Haahr S 40
Hamazaki K 32
Hammer GS 1
Hansen B 65
Hansen NE 41
Hansen PW 8
Hassan ZM 91
Hassett J 1
Hasui K 39
Havele C 107
Heit W 99
Henderson EE 15
Herberman RB 14
Herberman RB 42
Hermina NS 66
Hersey P 23
Higuchi Y 32
Hirao F 90
Hirschman SZ 1
Hirt B 60
Hitsumoto Y 115
Hobbs A 23
Hoffbrand AV 20
Holzman RS 3
Hong R 11
Honn KV 72
Hoover EA 51
Houchens DP 85
Huard TK 102
Hwang-Chen SP 106
Ievleva ES 108
Ihle JN 59
Inawashiro M 27
Ip SH 8
Ito S 46
Iwado T 32
Iwai N 30
Izumi T 28
Jakab A 37
Jakobisiak M 101
James K 65
Jankowiak S 34
Janossy G 103
Janossy G 20
Janowska-Wieczo 101
Jansen J 10
Jehn U 113
Jensen FC 48
Jerrells T 14
Jimbow K 13
Jondal M 77
Juillard GJ 54
Kajikawa K 17

Kamisaku H 47
Kantoch M 101
Kaplan NO 48
Karavodin LM 24
Karjalainen HE 116
Karle H 41
Kavai M 37
Kawase I 90
Kay NE 22
Kazmers IS 73
Kefford RF 69
Kelley WN 73
Kempf J 70
Kenwrick S 44
Ketcham A 31
Kim JC 52
Kitagawa N 30
Kitaichi M 28
Kitamura T 17
Kociba GJ 51
Kojima O 30
Konaga E 32
Koo GC 87
Kornfeld SJ 1
Koziner B 81
Krech R 56
Kubanel B 99
Kubo E 47
Kung PC 105
Kurec AS 112
Landegren U 26
Lange M 3
Lannom RA 48
Larsson SE 50
Lasek W 101
Leben L 57
Lee JC 59
Lee LF 55
Lenkey A 37
Lin ST 5
Lin TY 5
Linker-Israeli 104
Lipsick JS 48
LoBuglio AF 102
Lohmann-Matthes 94
Lopez C 1
Loseva MI 35
Louis JA 60
Lundgren E 50
Lydyard PM 18
Majima S 30
Mannami T 32
Mantyjarvi RA 116
Marczak M 101
Markowska J 34
Marnett LJ 72
Martin LN 52
Maruotti RA 16
Masuda S 17
Masuno T 90
Masur H 3
Matsui T 32
Matutes E 6
McCarthy WH 23
McGovern VJ 23
Mechetner EB 108
Meo C 109
Meretey K 37
Merrill J 77
Mertelsmann R 81
Mescher MF 114
Messner HA 83
Metcalf D 75
Michelis MA 3
Mickshe M 38
Milili M 80
Mimura H 32
Minamishima Y 115
Misz M 37
Mitchell BS 73
Miwa H 32
Moller-Larsen A 40
Moolten FL 63
Moolten FL 71
Moore MA 81
Mori S 27
Moriizumi T 17
Morita T 46
Moritani Y 32
Mosca JD 15
Mosmann TR 107
Mrackova E 7
Mugitani H 29
Munakata H 46
Munck A 67
Murray HW 3
Muto M 47
Nadji M 68
Nakanishi I 17
Namba M 90
Ney P 11
Nickells MW 100
Nicola NA 75
Nishikawa H 90
Nishio C 13
Nishioka B 30
Nomoto K 89
Novogrodsky A 64
O'Dorisio MS 66
O'Dorisio TM 66
Oblakowski P 101
Ogura T 90
Oh SK 63
Oh SK 71
Okamoto K 27
Oken MM 22
Olsen RG 51
Onorato I 3
Orita K 32
Orn A 26
Orn A 76
Oseto M 115
Ostrand-Rosenbe 111
Otsuka S 29
Ovejera AA 85
Paetkau V 107
Pal A 37
Paman RL 54
Parham DM 1
Parmiani G 58
Paul RD 68
Pavlovsky S 12
Perlin E 14
Peterson C 88
Pezzuoli G 16
Pfleiderer W 15
Potter CW 91
Powell RG 18
Purtilo DT 8
Puskas E 37
Ralph P 81
Ramstedt U 26
Rangan SR 52
Rebar L 59
Rees RC 91
Reichenbach NL 15
Reid J 14
Rey A 110
Rey A 93
Riccardi C 42
Rich IN 99
Ritzel G 107
Robb RJ 67
Roberts JA 52
Rochette-Egly C 70
Rodriguez-Valve 33
Roviaro G 16
Rozinova EN 108
Rubin AL 64
Rucheton M 110
Ruhl H 21
Sado T 47
Saiz-Garcia F 33
Sakamoto K 8
Sakatani M 90
Sakiyama Y 84
Sanger VL 55
Santoni A 42
Sartori F 16
Sasaki M 46
Sato E 39
Sawada Y 15
Saxon A 4
Schanker HM 4
Schiff C 80
Schmidt W 57
Schroder H 40
Schroff R 4
Schroit AJ 98
Seeley J 8
Serrou B 110
Serrou B 93
Sharma JM 55
Shinbo T 29
Sieber G 21
Siegal FP 1
Siegel M 1
Simm S 34
Skovmann-Sorens 40
Smith KA 67
Sonoda S 115
Sosnowska M 101
Steinmann G 81
Stenson WF 100
Stenzel KH 64
Stiehm M 81
Stigbrand T 50
Stouwe RA 3
Stutman O 82
Suhadolnik RJ 15
Suzuki K 27
Sweny P 20
Szabo T 37

Szegedi G 37
Takami S 115
Terasaki PI 104
Thiel E 113
Thierry C 110
Tomaszkiewicz T 34
Torok K 37
Tosner J 36
Townsend LB 73
Tribukait B 88
Tsang KY 45
Uchida A 38
Ullberg M 77
Utsumi S 115
Valles H 110
Varano A 87
Varoli F 16
Vejbora O 36
Wang YM 5
Watanabe T 32
Wayner EA 44
Webb PJ 44
Wechsler A 6
Weisman JD 4
Wigzell H 26
Wigzell H 76
Winblad B 50
Windsor NT 61
Withers HR 31
Wolf RA 4
Worman CP 18
Wormser G 3
Wotring LL 73
Wu JM 15
Yagi Y 39
Yamada Y 95
Yamada Y 96
Yamada Y 97
Yamamura Y 45
Yamane T 30
Yanbe H 13
Yang TJ 53
Yata J 29
Yoshimoto T 90
Young NS 106
Zagury D 110
Zahringer M 94
Zanjani E 99
Zannini P 16
Zarling JM 105
Zavazal V 7
Zerban H 56
Zubler RH 60
Zwaan FE 10

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In this issue:

- **EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS** **1-48**
- **EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS** **49-67**
- **EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION** **68-110**
- **THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE** **111-120**
- **ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY** **121**
- **RELATED BIOLOGY OF IMMUNE CELLS** **122-133**
- **CMI METHODOLOGY** **134-140**
- **SUPPRESSOR CELL ACTIVITY** **141-143**
- **OTHER RELATED STUDIES** **144-145**

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EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. CIRCULATING IMMUNE COMPLEX AND IMMUNOLOGIC RESPONSES IN PATIENTS WITH MALIGNANT TUMORS.

Saiga T
First Dept. Surgery, Sch. Medicine, Gifu Univ., Tsukasa-cho, Gifu 500, Japan
Nippon Geka Gakkai Zasshi; 82(6):587-598 1981

One hundred forty-four patients with malignant tumors (gastric cancer, 60 patients; colorectal cancer, 42 patients; lung cancer, 32 patients; and breast cancer, 10 patients) were examine d for circulating immune complex (CIC) by C1q solid-phase radioimmunoassay. They were tested for cellular and humoral immunity at the same time and the correlation of the responses with CIC was investigated. Positive CIC was obtained in 16 of the patients (11.1%), a high incidence being noted in patients with advanced cancer. Two of the 13 patients from whom the tumor was not completely removed showed persistent positive CIC postoperatively. The positive rate for delayed skin tests (tuberculin test and phytohemagglutinin response) was higher in patients with positive CIC than in those with negative CIC. No significant difference was observed in the T cell and B cell content between the positive CIC group and the negative CIC group, before or after surgery. Blast formation of lymphocytes showed a tendency to be lower in the positive CIC group than in the negative CIC group, before or after surgery. However, no significant difference was noted. No significant difference was observed in the CH50, C3 and C4 complement systems between the positive and negative CIC groups before surgery. After the operation, the positive CIC group had significantly higher C4 levels than the negative CIC group. No significant difference was observed in serum glycoproteins (alpha1-acid glycoprotein, alpha1-antitrypsin and haptoglobin) between the positive CIC group and the negative group, before or after surgery. Although CIC caused no significant differences in cellular immunity or humoral immunity, it is considered to be a factor which has some influence on them. (48 Refs) (In JPN)

2. IMPORTANCE OF THE IMMUNOLOGICAL STUDY IN THE PROGNOSIS OF A CANCER PATIENT.

Barg S, Levin M, Rezzonico R
Departamento de Cirugia, Hopital de Agudos Jose Maria Ramos Mejia, Urquiza 609, Buenos Aires, Argentina
Cell Mol Biol; 27(5):563-569 1981

This work deals with the experience collected at the Department of Surgery of the Hospital de Agudos Jose Maria Ramos Mejia, from 1970 to 1977. Patients (1043) were evaluated from an immunological point of view: 803 bearing neoplastic diseases with different sites and stages. These were compared with 156 patients with benign pathology and with 84 healthy people. Cell-mediated and humoral immunity were evaluated. This was carried out before any kind of treatment was applied to the patients, being repeated each 3 or 6 mo as control of their disease. The initial immunological evaluation was good in 37% of the patients with neoplastic diseases, in 56% of those with benign pathology and in 72% of the healthy people. The coincidence between the immunological profile and the evolution of the neoplastic disease was of 65%, based on EORTC's criteria. The coincidence of four positive tests was of 4% in neoplastic diseases, against 17% in patients with benign pathology and 44% in healthy people. The biological tests showed an immunodeficiency of 12% of blast transformation in patients with advanced cancers, against 37% in localized cancers for a normal average of 40%; E-rosette test, 17% and 40.1%, respectively, for a normal average of 41.1%; EAC-rosette test, 8% in advanced neoplastic diseases and 14% in localized cancers for a normal average of 19.2%; and membrane immunoglobulins, 14% and 19%, respectively, for a normal average of 21.8%. (Author abstract) (29 Refs)

3. DEFECTIVE IMMUNOREGULATORY T-CELL FUNCTION IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Han T, Ozer H, Henderson ES, Dadey B, Nussbaum-Blumenson A, Barcos M
Medical Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Blood; 58(6):1182-1189 1981

Chronic lymphocytic leukemia (CLL) of B-cell origin results in the malignant proliferation of small Ig-bearing lymphocytes. There is currently a controversy in the literature regarding both the ability of this leukemic population to differentiate into mature plasma cells, as well as the ability of apparently normal T cells from these patients to regulate allogeneic B-cell differentiation. In the present study we have examined the lymphocytes of CLL patients in various clinical stages of their disease and with different surface phenotypes of their leukemic B-cell population. Our results show that leukemic CLL B cells from all 20 patients (including 1 patient with a monoclonal IgM paraprotein and another with a monoclonal IgG paraprotein) are incapable of further differentiation even in the absence of suppressor T cells and the presence of helper T lymphocytes. This lack of capacity to differentiate is unaffected by clinical stage, by therapy, or by the phenotype of the malignant population. Since the leukemic B population did not suppress normal allogeneic B-cell differentiation, the maturation deficit is evidently intrinsic to the leukemic clone rather than a result of activity of non-T suppressor cells. T helper function was also variably depressed in the blood of some patients with CLL, and this depression did not correlate with clinical stage, with therapy, or with the degree of lymphocytosis. Dysfunction of radiosensitive T suppressor cells was found to be the most consistent regulatory deficit of CLL T cells. Each of 11 patients whose leukemic cell population was of the mudelta, mualpha, or mu phenotype had both helper and suppressor cell defects. In contrast, three patients with gamma-bearing leukemic populations exhibited normal T helper as well as normal radiosensitive suppressor T-cell function. These results emphasize the heterogeneity of immunoregulatory T-cell function in patients with CLL and may indicate immunologically unique subgroups of patients with this malignancy. (Author abstract) (18 Refs)

4. ACID PHOSPHATASE STAINING PATTERN AS AN INDICATOR OF T-CELL ACUTE LEUKEMIA.

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Am J Clin Pathol; 76(6):760-764 1981

Acid phosphatase staining pattern has been variably advocated and discouraged as an indicator of T-cell differentiation of acute lymphoblastic leukemias. This study indicates that acid phosphatase staining pattern will correlate with the results of E rosette testing in both T-cell and non-T, non-B acute lymphoblastic leukemias in over 90% of cases. Acid phosphatase staining pattern may reliably be used to indicate T-cell differentiation in acute lymphoblastic leukemia in cases where insufficient material for E rosette testing is available. (Author abstract) (10 Refs)

5. IN VITRO AND IN VIVO NK CELL MODULATION BY BIOLOGICAL RESPONSE MODIFIERS (BRM) IN CANCER PATIENTS (MEETING ABSTRACT).

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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Many recent data suggest that non immunodepressed patients respond better to chemotherapy than immunodepressed patients. This fact, closely related to the immune imbalance of the cancer patient, of itself justifies the recent interest in BRM. In vitro and in vivo in immunodepressed solid tumor bearing patients, we evaluated the immunorestorative potential of 5 BRM: human fibroblast interferon (HFIF) injected IV, Bestatin purified from Streptomyces olivoreticuli, NPT 95 392 which is a new Isoprinosine derivative, RO 95132 a retinoic acid derivative. These BRM were used for 3 wk and all parameters were evaluated before and after treatment. At the doses used, no BRM presented major side effects (hepatic or renal dysfunction, blood pressure, cardiac function, hematological modification). Natural killer (NK) activity showed significant changes for all drugs, although NK activity significantly increased only after HFIF and Bestatin. These results underline the increasing attention being given to these BRM which are now just entering phase 3 studies as adjuvant therapy (Bestatin), or phase 2 studies either alone (HFIF) or associated with chemotherapy. (no Refs)

6. POSTOPERATIVE FOLLOW-UP OF NATURAL KILLER CELL ACTIVITY AND CEA IN PATIENTS WITH GASTROINTESTINAL CARCINOMA (MEETING ABSTRACT).

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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Recent studies have provided much evidence for the antitumor effect of Natural Killer (NK) cells. In this study it was examined, if the pre- and postoperative follow-up of NK cell activity shows a correlation to the carcinoembryonic antigen (CEA) level and the stage and the course of the disease. In 24 patients with gastrointestinal carcinoma the NK cell activity and the CEA serum concentrations was measured pre- and 4-8 wk postoperatively. In 10 patients multiple determinations could be performed up to 15 mo postoperatively. NK cell activity has been measured by a 51Cr release assay employing the human cell line K562. CEA serum concentration has been determined by radioimmunoassay. In 20/24 patients a positive correlation of the change of the NK cell activity, the CEA curve and the clinical stage of the disease was found. In potentially curative operated patients an increase of NK cell activity and a normalization of CEA values could be seen, in patients with tumor progression vice versa. By long term follow-up of both parameters we found even a higher positive correlation. Whether the NK cell activity or the CEA test is the more sensitive indicator concerning the early detection of tumor recurrence has to be examined in further studies. (no Refs)

7. THE SENSITIVITY OF CLONE-FORMING MYELOID LEUKAEMIA CELLS TO COLONY STIMULATING ACTIVITY: RELATION TO RESPONSE TO CHEMOTHERAPY (MEETING ABSTRACT).

Francis GE, Tuma GA, Berney JJ, Wing MA, Hoffbrand AV
Department of Haematology, Royal Free Hospital, London, England
Br J Haematol; 49(1):133 1981

The sensitivity of acute myeloid leukemia (AML) clone-forming cells to the specific regulator granulocyte-macrophage colony-stimulating activity (CSA) was determined in semi-solid agar cultures. The mean CSA threshold (amount of CSA required to stimulate 50% of the clone-forming cells) of 27 different AML cell samples varied from normal to an approx ninefold increase in CSA requirement. This disturbance of CSA sensitivity in the presentation marrow sample was found to be closely related to the response to induction chemotherapy. There was a highly significant correlation between the mean CSA threshold and the number of courses of chemotherapy required to induce remission. There was also significant correlation between the sensitivity to CSA and the ratio of decline of the percentage of bone marrow blasts following the first course of chemotherapy. Sensitivity of CSA was closely related to the clone size achieved in maximally stimulated cultures of AML cells and this in turn was found to be related to the remission rate and ease with which remission was achieved (analysis of presentation marrows from 39 patients). Possible reasons for the linking of these two properties of AML cells and their relation to response to therapy will be discussed. (no Refs)

8. PRE-T CHRONIC LYMPHOCYTIC LEUKEMIA WITH COMMON ACUTE LYMPHOBLASTIC LEUKEMIA ANTIGEN. A NEW IMMUNOLOGIC VARIANT.

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Am J Clin Pathol; 76(6):837-840 1981

Chronic lymphocytic leukemia (CLL) is a B cell disorder but occasionally may have the characteristics of a T cell and rarely as a dual T and B cell. A case of pre-T CLL with common acute lymphoblastic leukemia antigens is presented. The Markers Studies of the bone marrow lymphocytes were +HLA, +cALL, +EAC, +Ia, -TdT, -E and peripheral blood lymphocytes were +HTLA, +Ia, -cALL, -EAC, -TdT, -E. The poor course of our patient suggests that more detail subtyping of CLL to identify similar subtype may provide additional prognostic information. (Author abstract) (27 Refs)

9. UNUSUAL CHROMOSOMAL TRANSLOCATION, T(1P+,7Q-), AND FAMILIAL LEUKEMIA IN A PATIENT WITH CHRONIC MYELOMONOCYTIC LEUKEMIA.

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Conn Med; 45(12):767-771 1981

A single case of chronic myelomonocytic leukemia (CMML) occurring in a 68-yr-old man with an unusual chromosomal translocation t(p+,7q-) and a family history of adult leukemia is reported. Persistent monocytosis in peripheral blood, proliferation of immature myelocytes in the marrow, and high serum and urine lysozymes led to the diagnosis of CMML. The observed translocation was evident in peripheral blood and marrow myeloid cells in the latter part of the patient's 8 yr course of disease. Two of the patient's cousins had chronic lymphocytic leukemia, a sister had acute undifferentiated leukemia, and a grandson had Hodgkin's disease. Since analysis occurred subsequent to busulfan treatment, the possibility exists that the abnormal karyotype was caused by the action of the alkylating agent. Translocations such as that reported here, however, have not been observed in other series of patients receiving busulfan. (47 Refs)

10. TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE IN ADULT LYMPHOBLASTIC LEUKEMIA: RELATIONSHIP WITH BLAST CELL COUNT.

Baccarani M, Marini M, Bagnara G, Gobbi M, Saviotti F, Brunelli M, Tura S
Istituto di Istologia e Embriologia Generale, via Belmeloro, 8, 40126 Bologna, Italy
Haematologica (Pavia); 66(5):579-587 1981

The relationship of blast cell count to terminal deoxynucleotidyl transferase (TDT) levels were studied. Biochemical assays were carried out on the peripheral blood cells of 27 adult patients with acute lymphoblastic leukemia (ALL) TDT activity was positive in 18/19 patients with blast cell counts greater than 0.5 x 10(3)/ul. All patients who were positive when assayed for RBC rosette formation and for surface immunoglobulins were TDT positive. A number of patients with TDT positive blast cells were studied during induction therapy or at early relapse when their blast cell counts were lower than 0.5 x 10(3)/ul. In 11/20 assays, TDT was detectable in spite of the very low blast cell number. In patients presenting with 'oligoblastic' leukemia (mean blast cell count 0.15 x 10(3)/ul), the TDT assay was always negative. The comparison of results suggested that in the oligoblastic patients, TDT negativity was not merely due to the paucity of blast cells in the sample studied, but reflected a true absence or a very low level of enzyme activity. (13 Refs)

11. EPIDEMIOLOGY OF LYMPHOID MALIGNANCY. AN ETIOLOGICAL HYPOTHESIS OF ADULT T-CELL LEUKEMIA/LYMPHOMA.

Tajima K, Tominaga S
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Gan To Kagaku Ryoho; 8(7):1009-1016 1981

In order to study adult T-cell leukemia/lymphoma (ATLL), which is prevalent in Kyushu, an etiological hypothesis of ATLL is proposed. ATLL is found in limited zones in Kyushu, mainly in rural and coastal areas, which are warm in winter and humid in summer. The geographical distribution of filariasis which accompanies several lymphoreticular ailments and was prevalent until 20 yr ago, was found to be closely correlated with that of patients with ATLL. It was also suggested from analysis of the chronological changes in the av wt and height of school children by prefecture that the nutritional condition of the inhabitants of Kyushu might have been poorer than that of other districts, especially in the past. In these respects, it is conceivable that repeated exposure to filarial infection in association with undernourishment and some other factors might have played an important role in the etiology of ATLL. (30 Refs) (In JPN)

12. PRELEUKEMIA.

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Johns Hopkins Med J; 148(5):200-204 1981

Clinical features, pathogenesis, and treatment of the preleukemia syndrome (PLS) are reviewed and a case history presented. PLS possesses distinct clinical and diagnostic criteria. Some prerequisites include anemia and oval macrocytosis in peripheral blood (PB), megaloblastoid erythropoiesis and/or disorderly granulopoiesis, and absence of overt findings of leukemia in bone marrow (BM). Among corroborative findings are nucleated RBC, hypochromia, bizarre platelet size, and reduced platelets and neutrophils in PB; BM will show erythrocytic and megakaryocytic hyperplasia. Review of two recent prospective series indicates significant risk (20-25%) of development of acute nonlymphocytic leukemia in patients with PLS, with av time to acute leukemia of less than 2 yr. High excess mortality exists with these patients, especially due to infection or bleeding. A 52-yr-old male patient presented with a hematocrit of 24%, platelets of 14,000/cubic mm, and 2,400 WBC/cubic mm, with 3% blasts, 1% juveniles, no neutrophils, 87% lymphocytes, 5% monocytes, and 4% eosinophils. Thirteen nucleated RBC/100 WBC were counted, and hypochromasia was noted in the peripheral smear; striking anisocytosis and poikilocytosis with frequent oval macrocytes and microcytes were seen. BM showed hypercellularity, evidence of erythroid hyperplasia, rare megakaryocytes, abnormal erythropoiesis, arrest of myeloid maturation, and defective neutrophil granulation. The Diagnosis of PLS was confirmed and the patient was referred for treatment of acute leukemia. (25 Refs)

13. DECREASED SYNTHESIS OF HIGH-MOLECULAR-WEIGHT GLYCOPEPTIDES IN HUMAN PROMYELOCYTIC LEUKEMIC CELLS (HL-60) DURING PHORBOL ESTER-INDUCED MACROPHAGE DIFFERENTIATION.

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Cancer Res; 42(2):484-489 1982

The human promyelocytic leukemia cell line, HL-60, synthesized a class of high-mol-wt (MW 5,000 to 7,000), N-linked glycopeptides as the major class of protein-bound carbohydrates. Small glycopeptides (MW 2,500 to 3,500), typical of most mammalian cells except RBC, represented a minor component in these cells. The large glycopeptides were labeled efficiently with fucose, glucosamine, and galactose but only poorly with mannose. They were found not to be glycolipids, glycosaminoglycans, or mucin-type glycopeptides and were not susceptible to exoglycosidases, but they were partially degraded by endo-beta-galactosidase. These characteristics are similar to those of the large glycopeptides synthesized by RBC, by another human myeloid leukemia cell line (K562), and by human and murine teratocarcinoma cells. High-mol-wt glycopeptides predominated on another human myeloid leukemia cell line KG1, but they were expressed at low levels on both a human monocytic leukemia cell line (THP-1) and a human T-lymphoblastoid cell line (Jurkat). when HL-60 cells were induced to differentiate into macrophage-like cells with phorbol esters, the proportion of large glycopeptides decreased, and the production of small glycopeptides predominated. This shift was observed within the first several hr after exposure to phorbol esters and was temporally related to the acquisition of adherent properties by the induced cells. In contrast, when HL-60 cells were induced to differentiate into granulocytes by dimethyl sulfoxide, hypoxanthine, or retinoic acid, they continued to synthesize glycopeptides similar to uninduced cells. Human peripheral blood granulocytes synthesized primarily large glycopeptides, whereas monocytes and lymphocytes synthesized mostly small glycopeptides. These results indicate that the synthesis of high-mol-wt glycopeptides is a property of human myeloid leukemia cell lines and that it persists throughout myeloid differentiation. A proportionate decrease in the synthesis of these large glycopeptides is a part of the differentiation program for monocytes and macrophages. (Author abstract) (34 Refs)

14. IN VITRO REVERSAL OF DEPRESSED T-LYMPHOCYTE FUNCTION IN THE PERIPHERAL BLOOD OF BRAIN TUMOR PATIENTS.

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JNCI; 68(1):27-33 1982

Peripheral blood mononuclear cells from some brain tumor patients exhibited depressed T-lymphocyte responses to the polyclonal mitogen phytohemagglutinin (PHA). These responses, initially depressed, were restored to near normal by a 24-hour preculture in growth medium. The effect of preculture was mimicked by mild trypsinization before addition of PHA. In addition, cells treated with deaggregated antihuman IgG resulted in greatly reduced responses to mitogen by mononuclear cells from all brain tumor patients. Anti-IgG had no effect if cells were precultured for 24 hours. The results suggest that, in brain tumor patients, depressed immune function associated with tumor progression was caused by suppressor cells which were activated by humoral factors that express IgG antigenic determinants. (Author abstract) (18 Refs)

15. CHANGES IN LYMPHOCYTES AS AN EARLY SIGN OF RELAPSE IN ADULT ACUTE LEUKEMIA.

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First Dept. Internal Medicine, Hirosaki Univ. Sch. Medicine, Hirosaki 036, Japan

Tohoku J Exp Med; 135(3):237-245 1981

Laboratory tests were administered to 23 patients (17 males, 6 females; 18-53 yr old) during the remission phase of leukemia (15 acute myelocytic; 8 acute lymphocytic) until relapse occurred, and an attempt was made to correlate test result changes with the onset of relapse. Blood examinations consisted of total protein, albumin/globulin ratio, lactate dehydrogenase activity, zinc sulfate test, erythrocyte sedimentation rate, C-reactive protein, and immunoglobulin levels (IgG, IgA, IgM), determined once during remission and once during relapse. Red cell counts, white cell counts with differential hemoglobin levels, platelet counts, and reticulocyte counts in the peripheral blood were done every 2 wk after remission until relapse. T-cells and B-cells were counted by E-rosette and EAC-rosette formation; blastogenesis of lymphocytes was measured by 3H-uridine incorporation after stimulation with phytohemagglutinin-P. Bone marrow cells aspirated from the sternum and ilium were cultured. Neither laboratory blood tests nor blood counts showed significant changes in association with relapse. Bone marrow cultures did not show significant differences either, but percentages of both T- and B-cells had decreased markedly at the time of relapse . A decrease in T- and B-lymphocytes or an increase in peripheral blood lymphocytes greater than 40-50% during maintenance therapy indicates the need for immediate bone marrow puncture. (15 Refs)

16. ROLE OF CELLULAR IMMUNITY IN RELATION THE SPECIFIC HEMATOLOGICAL FEATURES IN TYPICAL LEUKEMIA.

Takahashi T, Nakayama S, Hoshino T

Second Dept. Internal Medicine, Kyoto Univ., Kyoto, Japan

Rinsho Ketsueki; 22(6):792-800 1981

The role of immunocompetent cells in the development of unusual and unique hematological features of atypical leukemia was studied. A well-preserved hypersensitivity reaction to recall antigen was demonstrated by a higher rate of positive tuberculin tests than in overt leukemia. Despite lymphocytopenia, circulating lymphocytes exhibited normal proportions of T cell subsets and normal phytomitogen responsiveness. Residual physiological suppressor cells were observed. Suppressor lymphocytes were induced in response to various types of immunologic stimulation, including blood transfusion: co-cultured patient circulating lymphocytes suppressed growth of allogeneic normal culture colony forming units (CFU-C) and pokeweed mitogen-induced immunoglobulin production of allogeneic normal lymphocytes. An intercellular control mechanism between immunocompetent cells and a leukemia clone of atypical leukemia was suggested by the suppression of abnormal CFU-C colony and cluster formations by co-cultured autologous T-cells. Atypical leukemia cells showed persistent natural killer effector activity. (13 Refs) (In JPN)

17. IMMUNOCOMPETENCE AND MALIGNANT LYMPHOMA: IMMUNOLOGIC STATUS BEFORE THERAPY.

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Cancer; 48(12):2702-2709 1981

One-hundred-eighty-six previously untreated patients with malignant lymphoma were evaluated for immunocompetence by means of several tests of immune function: total circulating lymphocytes, T cells (E-rosettes), B cells (EAC-rosettes), delayed hypersensitivity to six recall antigens, serum immunoglobulins, mixed lymphocyte culture, and lymphocyte mitogenic response to phytohemagglutinin and pokeweed mitogen. The results were correlated with histology, stage, and clinical features. Diffuse lymphomas, especially diffuse histiocytic (large cell) (DHL), were associated with decreased absolute lymphocytes and E-rosette forming cells. Skin test reactivity varied with both histology and stage. For example, only one of six tests was impaired in diffuse lymphocytic well differentiated (DLWD) lymphoma in contrast to two of six in localized DHL and five of six in advanced DHL. Patients with nodular lymphoma exhibited depressed mean levels of IgA and IgG, while only IgA was significantly decreased in diffuse lymphoma. Mitogen stimulation was depressed in all groups, although mixed lymphocyte cultures did not differ significantly from controls. In summary, there is a spectrum of immunodeficiency of both B and T cell type in patients with malignant lymphoma that correlates with histology and stage. Implications and possible mechanisms of these observations are discussed. (Author abstract) (25 Refs)

18. THE PATHOPHYSIOLOGY OF MALIGNANT LYMPHOMA FROM THE HEMATOLOGICAL POINT OF VIEW: (1) THE LEUKEMIC TRANSFORMATION OF MALIGNANT LYMPHOMA, ESPECIALLY TRADITIONAL 'RETICULUM CELL SARCOMA'.

Kinoshita K, Amagasaki T, Yamada Y, Kamihira S, Muta T, Kitamura T, Ikeda S

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Nippon Ketsueki Gakkai Zasshi; 44(6):1169-1177 1981

The size of leukemic cells in 15 cases of traditional 'reticulum cell sarcoma' with leukemic manifestation was measured. Almost all cases were of T-cell origin in nature on the basis of spontaneous rosette formation with sheep erythrocytes (E-rosettes) and cell morphology. As the result, they were divided into the small cell dominant group (8 cases) and the large cell dominant group (7 cases), respectively. In the former more than 80% of the leukemic cells in the peripheral blood were less than 12 u in cell diameter and in the latter more than 50% of the leukemic cells were larger than 15 u in size. In the small cell dominant group, the majority of the peripheral leukemic cells showed the obvious lymphocytic differentiation with condensed nuclear chromatin and scant cytoplasm, although in many of the cases lymphomatous infiltrate was characterized by large or pleomorphic lymphoid cells, accompanied by the proliferation of post capillary venule-like vessels (PCV) and transmural migration of small abnormal lymphoid cells. The clinicohematological features were similar to those of so-called 'Adult T-cell leukemia' in Japan. On the other hand, the large cell dominant group showed the histology of monotonous infiltrate of large lymphoid cells without the proliferation of PCV and transmural migration of the lymphoid cells. Hematological examination revealed that the leukemic cells were large blastic cells with basophilic cytoplasm and they did not increase to such a degree that WBC count was markedly elevated. The clinical features were lymphomatous presentation with massive lymphadenopathy. The mechanism of leukemic manifestation is also discussed. (Author abstract) (30 Refs) (In JPN)

19. EFFECT OF PARENTERAL NUTRITION ON IMMUNE STATUS OF PATIENTS SUBJECTED TO SURGERY FOR CANCER OF THE STOMACH.

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Vestn Khir; 127(10):24-28 1981

The effect of parenteral nutrition on immune status was studied in 48 patients (30 men, 18 women; 30-70 yr old) subjected to subtotal stomach resection for cancer of the stomach. Within 3-5 days after the surgery, 24 patients (Group I) received complete parenteral nutrition with amino acid mixtures, lipid emulsions, glucose, and electrolyte soln, while 24 other patients (Group II) received conventional infusions of glucose and electrolyte soln. The complete parenteral nutrition did not affect the number of T-lymphocytes. The patients in Group I showed increases in levels of IgG and IgM, while the patients in Group II showed decreases in these levels throughout the entire postoperative period. Postoperative complications (pneumonia, abscess, phlegmon) were observed in 4/24 patients in Group I and in 6/24 in Group II. (3 Refs) (In RUS)

20. A STUDY OF CELL-MEDIATED IMMUNITY TO GASTROINTESTINAL CANCER.

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Cell Mol Biol; 27(2/3):119-131 1981

The following results were obtained from our study on cell-mediated immunity of gastrointestinal cancer: (1) The PPD and PHA skin test, the percentage and absolute number of peripheral T lymphocytes and blastogenesis rate of peripheral lymphocytes by PHA in cancer cases were obviously lower than those in gastroduodenal ulcer cases and healthy adults. (2) The PPD skin test, the percentage of peripheral T lymphocytes and the blastogenesis rate of peripheral lymphocytes by PHA in gastric cancer cases decrease as the clinical stage advances. These results have brought us the fact that to know the preoperative patient's immunity to the carcinoma can be one of the criteria to find out its stage and the operation method. (Author abstract) (11 Refs)

21. TUMOR-ASSOCIATED CELL-MEDIATED IMMUNE RESPONSE OF GASTRIC CANCER PATIENTS: WITH PARTICULAR EMPHASIS ON CORRELATION WITH TUMOR BURDEN AND EFFECTS OF SURGICAL TUMOR REMOVAL.

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First Dept. Surgery, Sch. Medicine, Chiba Univ., Chiba, Japan

Nippon Gan Chiryo Gakkai Shi; 16(4):673-680 1981

Lymphoproliferative (LP) responses by allogeneic tumor extracts were compared with autologous responses to confirm the existence of common tumor-associated antigens (TAA) in gastric cancer (GC). The relationship between tumor burden and tumor-specific cellular immune response in GC was evaluated. The effect of surgical tumor removal upon tumor-specific cellular immune response was studied. Allogeneic TAA-induced LP responses of 38 GC patients were significantly superior (p less than 0.10) to those of normal subjects. Both allogeneic and autologous responses of resectable GC patients were remarkably superior (p less than 0.05) to those of normal persons, but no differences were found differences in av cancer specific stimulation index and ratio of autologous to allogeneic positive responses. Five of six GC patients with a positive response to autologous TAA had similarly positive responses to allogeneic TAA. Five of eight GC patients with a positive response to allogeneic TAA responded similarly to autologous TAA. The LP responses of the GC patients to allogeneic TAA were tested preoperatively and evaluated according to the clinical stage determined from the operative findings. The mean LP responses for stages I-IV were 1.14 +-0.25. 1.75 +-0.64, 1.92 +-0.87, and 0.93 +-0.21, respectively. Responses of all GC patients, including those with positive preoperative LP, decreased to within normal range 1 wk after resection and were virtually nil 1 mo after surgery. (22 Refs)

22. PERIPHERAL, MUCOSAL, AND TUMOUR-INFILTRATING COMPONENTS OF CELLULAR IMMUNITY IN CANCER OF THE LARGE BOWEL.

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Gut; 22(9):744-751 1981

A reliable technique has been devised for the preparation of colorectal tumor-infiltrating lymphocytes (TIL). The immune capacity of these lymphocytes has been assessed in vitro and compared with that of lymphocytes infiltrating the lamina propria of adjacent normal mucosa (LPL) and with autologous peripheral blood lymphocytes (PBL). Assay of natural killer cell function revealed the absence of such activity in TIL and LPL despite the presence of normal levels of PBL. Antibody-dependent (K cell) cytotoxicity activity was also absent in TIL and LPL. Both TIL and LPL showed significant mitogen-induced cytotoxic responses, although higher levels were detected in PBL. Tumor-infiltrating lymphocytes revealed depressed levels of spontaneous DNA synthesis, but mitogen stimulation of TIL was equivalent to that of LPL. T-cell proportions in TIL preparations were equivalent to those in PBL, but LPL comprised significantly fewer T cells. (Author abstract) (24 Refs)

23. NON-HODGKIN'S LYMPHOMAS: NOSOLOGY AND CLINICAL STUDY.

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Rev Prat; 31(47):3315-3331 1981

Diagnosis, classification, course, and treatment of non-Hodgkin's lymphomas (NHL) are described. The development of terminology for the description of NHL and Hodgkin's lymphomas is described. Cellular markers have allowed the identification of four types of NHL: nodular, diffuse, T-cell, and macrophage-derived NHL. Histological study is indispensable for the diagnosis, prognosis, and treatment of NHL although the role of cytological studies is not negligible. Clinical aspects, disease course, and treatment of nodular (NL) and diffuse (DL) large cell lymphomas are discussed. NL, accounting for 40% of NHL, is usually characterized by polyadenopathy. Extralymphatic involvement may include the abdominal cavity (80% of cases), bone marrow (60%), and rarely the mediastinum. NL progresses slowly; long survival does not necessarily require achievement of remission. Moderate chemotherapy and polychemotherapy are most useful in the treatment of NL. The most common symptom associated with DL is adenopathy, often limited to cervical and axillary regions and rarely involvement of mediastinal or sub-diaphragmatic areas. Complete remission, usually induced by polychemotherapy (endoxan, vincristine, prednisone), is absolutely necessary for survival in patients with DL. Radiotherapy provides the basis for treatment of localized forms of DL. Treatments for Stages I and II and Stages III and IV DL are described. The clinical course and treatment of lymphoblastic NHL and non-African Burkitt's lymphoma are described. (13 Refs) (In FRE)

24. MALIGNANT LYMPHOMA OF THE CNS - A CASE REPORT WITH PATHOLOGICAL AND IMMUNOLOGICAL STUDIES.

Suzuki M, Sato T, Komatsu S, Kimura N, Wada T
Dept. Neurosurgery, Sendai Natl. Hosp, Sendai, Japan
No Shinkei Geka; 9(11):1279-1284 1981

A 43-yr-old man underwent a surgical total removal of a tumor followed by radiotherapy (a total of 6,000 rad of 60Co) and chemotherapy. In the preoperative CT scan, a well-defined, nodular-shaped tumor was found in the left parietal region. This tumor disappeared when the combination treatment had been completed. Subsequently, CT scan demonstrated multifocal tumors with involvement of the roof of the fourth ventricle, frontal cortex and lateral ventricle. The patient expired 20 mo after the onset of symptoms. The tumors in the frontal lobes, left thalamus and subdural space of the upper cervical cord showed dense sheets of polymorphous, large to medium-sized lymphocytes. The microscopic findings were interpreted as showing malignant lymphoma, lymphocytic, poorly differentiated, and diffuse. Immunologically, E rosettes were formed by sheep red blood cells around the tumor cells. Immunofluorescence technique failed to demonstrate IgG, IgM and/or IgA in the cytoplasm of the tumor cells. By scanning electron microscopy, the tumor cells were devoid of microvilli. (Author abstract) (13 Refs) (In JPN)

25. INDICES OF CELLULAR IMMUNITY IN LUNG CANCER PATIENTS AFTER SURGICAL AND COMBINED TREATMENT.

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Sov Med; (10):33-36 1981

The effect of treatment on the state of cellular immunity was studied in 100 lung cancer patients (96 men, 4 women; 40-69 yr old). Among these patients, 29 underwent surgery alone, 34 received preoperative radiotherapy (300 rads, 5x/wk, total dose 3,600 rads), and 37 received postoperative radiotherapy (dosage and schedule as above). Immunological status was assessed prior to, during, and 6 and 12 mo after the treatment. Prior to the treatment, the lung cancer patients showed significant decrease of the indices of blast-transformation reaction (33% vs 50% in healthy controls), the number of rosette-forming cells (38% vs 53.9%), and absolute count of T-lymphocytes (733 vs 1,202). A more intensive normalization of the indices of cellular immunity was observed in the patients subjected to surgery alone or to surgery with preoperative radiotherapy. (8 Refs) (In RUS)

26. EFFECT OF RADIOTHERAPY ON THE IMMUNOCOMPETENCE IN PATIENTS WITH BRONCHOGENIC CARCINOMA AND LARYNGEAL CANCER.

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Nippon Igaku Hoshasen Gakkai Zasshi; 41(9):873-886 1981

We evaluated the immunocompetence of 80 patients with bronchogenic carcinoma and 17 patients with laryngeal cancer undergoing radiotherapy, using collectively many types of immunological parameters. In patients with bronchogenic carcinoma, no significant difference was seen with PHA and PPD skin tests, but the reactivity of PHA skin tests gradually decreased in the course of treatment. It was assumed that radiotherapy might not interfere with the recognition of antigen.

Lymphocyte blastoid transformations with PHA, ConA and PWM were all inhibited significantly. Since these three mitogens can stimulate the different groups of lymphocyte, the inhibition to the proliferative function of lymphocyte due to radiotherapy would seem to cover a wide area, including T and B lymphocyte. Concerning the comparative radiosensitivity of T and B lymphocyte, no significant result was obtained. However, in the dose of 20Gy the percentage of T lymphocyte decreased, while the percentage of B lymphocyte increased. The percentage of early rosettes, one subset of T cell, decreased more sensitively than that of T cell, but there was no significant difference. The percentage of IgGFcR(+)T cell, considered a part of cytotoxic T cell or suppressor T cell, decreased significantly in the dose of 20 Gy, but returned to a high value in the dose of 40Gy. As the helper T cell can be considered radioresistant, it has been suggested that radiotherapy might give the host an immunological enhancement against tumor if a certain suitable method is used. Immunocompetence of cases in Stage III, which was significantly high before treatment, decreased to the same level as those in Stage IV according to the treatment. In patients with laryngeal cancer, lymphocyte counts and reactivity of PHA skin tests were not influenced by radiotherapy, and then reactivity of PPD skin tests and lymphocyte blastoid transformations with PHA and ConA tended to increase instead. Those results seemed to come mainly from the removal of inhibition to the immune system due to tumor, so we hope the estimate of immunocompetence can bring us influential information for judgement of the time of recurrence. (Author abstract) (64 Refs) (In JPN)

27. PROGNOSTIC SIGNIFICANCE OF IMMUNOLOGICAL TESTS IN LUNG CANCER.

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Clin Exp Immunol; 43(2):362-369 1981

The prognostic significance of several immunological parameters was studied in 94 cases of lung cancer. Blood samples were obtained from 71 patients with newly-diagnosed non-oat cell carcinoma (NOCC) prior to treatment (including 39 with squamous cell carcinoma, 27 with adenocarcinoma, and 5 with undifferentiated carcinoma) and from 23 patients with unresectable bronchogenic NOCC that had been treated prior to the study. Parameters measured included percentage of lymphocytes in gradient-derived cell suspension (%LG), WBC count, lymphocyte (LC) count, percentage of E-rosette formation (ERF) at 4 C or 37 C, response to pokeweed mitogen (PWM), and response to concanavalin A (Con A). The greatest significance was shown by %LG, which decreased with advancing disease stage. WBC and LC counts and ERF showed no significant change. PWM response decreased significantly and Con A decreased insignificantly; analysis of results of test pairing suggested that PWM and Con A responses are dependent on %LG. The prognostic value of %LG was significant for the total number of patients and for those within a given stage. Median survival times (MST) for patients with resectable tumors were well beyond 12 mo for those with 60%LG and 12 mo for those with 40%LG. MST for patients with unresectable tumors were 5.5 mo for those with 60% LG and 4.2 mo for those with 40% LG. Analysis of cell buoyant density indicated that decreased %LG resulted from decreased density of nonlymphoid cells. Measurement of %LG was confirmed as a simple prognostic indicator. (39 Refs)

28. IMMUNE IMBALANCE AND IMMUNE MODULATION IN SOLID TUMOR PATIENTS: NEW INSIGHTS.

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Recent Results Cancer Res; 80:9-16 1982

Immune status in patients with solid tumors is reviewed. Several studies have found a variety of immunocomplexes (IC) that are present in increasing amounts during tumor growth or relapse (TGR) and in decreasing amounts following tumor reduction (TR). Because these complexes are apparently varied and poorly defined, practical use of IC measurements is limited. Changes in the plasma membrane lipid bilayer of WBC occur during TGR and disappear during TR. Plasma microviscosity may change in a similar fashion. Studies of patients treated with BCG have indicated that those with high levels of anti-BCG antibodies generally have a good prognosis, while those with low levels have a poor prognosis. A similar correlation has been found for vitamin A. Vitamin A apparently plays a role in cell differentiation and immune response. The T-gamma lymphocyte/T-mu lymphocyte ratio in patients increases during TGR and decreases during TR. A T-theophylline-resistant lymphocyte population that forms autologous rosettes is reduced during TGR and increases during TR. Suppressor-cell activity is affected by antiprostaglandins or irradiation and has therapeutic implications. Of new immunomodulating drugs, bestatin has antitumor activity in mice and RO-109359 increases cutaneous delayed hypersensitivity; results with interferon are unclear. (28 Refs)

29. IMMUNOLOGICALLY DEFINED PROGNOSTIC SUBGROUPS AS PREDICTORS OF RESPONSE TO BCG IMMUNOTHERAPY.

Reid JW, Cannon GB, Perlin E, Blom J, Connor R, Herberman RB
Naval Regional Medical Center, Box 666, Portsmouth, VA, 23708
Recent Results Cancer Res; 80:219-226 1982

Fifty-two Stage I and II patients with non-small cell lung cancer were randomized after resection to no further therapy, BCG, or BCG plus allogeneic tumor cells. Patients have been observed for 16-65 mo (mean 39.5). When the two immunotherapy arms were combined and plotted against controls, trend analysis suggested ($p = 0.088$) an increase in disease-free interval (DFI) only for Stage I patients. The one-way mixed lymphocyte culture (MLC) values were depressed in some patients prior to any immune stimulation. Immunotherapy significantly benefited DFI among patients with a depressed MLC. (Author abstract) (11 Refs)

30. IMMUNOSUPPRESSION RELATED TO THE ASCITIC FLUID IN PATIENTS WITH OVARIAN CARCINOMA (MEETING ABSTRACT).

Marotti T, Hrsak I, Krusic J, Deveric G
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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Humoral factors that suppress immune reactivity are present in the ascitic fluids of patients with cancer metastatic to the peritoneum. We have collected cell-free ascitic fluids from patients with ovarian carcinoma and assayed their ability to suppress the humoral immune response in mice. The data were correlated with other parameters of immune status (number of

T and B lymphocytes, phytohemagglutinin reactivity of lymphocytes, skin reactivity to recall antigens), with changes protein fractions in the sera and ascites and with the stage of disease. The immune response to sheep RBC was suppressed in mice injected with cell-free ascitic fluid from patients with ovarian carcinoma. The immunosuppressive effect of ascitic fluid obtained from stage IV patients was stronger than that of stage III patients. A good corr elation was found between the immunosuppressive effect in the mouse plague forming cells assay and the increased quantity of alpha-1 globulins in ascites. Skin areactivity to purified protein derivative also correlated with the immunosuppressive effect of ascitic fluid. However, the lymphocyte response to PHA and the numbers of E and EAC rosettes did not correlate either with skin reactivity to recall antigens, or with the suppression of plaque forming cells response in mice. (no Refs)

31. KINETIC CHARACTERISTICS OF MINIMAL TUMOR MASSES AND THEIR IMPLICATIONS FOR RATIONAL CHEMOTHERAPY.

Pileri A, Boccadoro M
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Haematologica (Pavia); 66(5):545-553 1981

The kinetics of the growth minimal tumor masses were studied in myeloma. Immunofluorescence and autoradiographic techniques showed that, in remission phase, the thymidine labelling index (LI) of monoclonal plasma cells was less than 1%. In remission phase, the LI was consistently lower than that observable during the clinical remission phase of the disease. The residual population was characterized by large numbers of monoclonal B lymphocytes, the reappearance of polyclonal plasmocytoid cells, a low degree of transition of monoclonal B lymphocytes to myeloma cells, a very low birth rate of the minimal myeloma cell population. It is suggested that the low proliferative activity of the residual tumor mass can easily account for the ineffectiveness of the standard maintenance therapy. Based on the growth kinetics of minimal tumor masses, post-remission strategies may use alternating drugs administered in progressively increasing dosages, progressively shorter intervals between doses of cytotoxic drugs, and greater use of non-cell cycle specific drugs capable of killing the resting cells. (19 Refs) (In ITA)

32. IMMUNOSUPPRESSION IN CANCER PATIENTS DURING RECURRENCE AND TERMINAL PHASE OF DISEASE (MEETING ABSTRACT).

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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Immune functions of 160 patients with or without recurrence of the malignant disease were examined during an observation time of 6 to 60 mo, before treatment, at time of recurrence and in some cases before the approaching death. As parameters the peripheral blood lymphocyte count, E and EAC rosette forming cells, lymphocyte proliferative responses to phytohemagglutinin, Concanavalin A and purified protein derivative, serum immunoglobulin levels and natural isohemagglutinins were applied. Functional tests proved to be more useful than enumeration of lymphocytes or their subpopulations: in spite of norm al number of lymphocytes the responses may be depressed. In patients with melanoma, a correlation could be seen between immunosuppression and recurrence rate of the disease. Such a correlation was not seen in breast cancer patients; however, the patients who originally had low immune responses had higher recurrence rate later on. (no Refs)

33. EMERGING IMMUNOLOGIC APPROACHES TO TREATMENT OF NEOPLASTIC DISEASES.

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Recent Results Cancer Res; 80:334-337 1982

Recent research on the immunobiology of the tumor-host relationship has demonstrated that nonspecific cellular immune reactions, like natural killer cells and cytotoxic autoreactive cells, may be far more potent antineoplastic mechanisms than specific T lymphocyte cytotoxicity. The hybridoma technique, making it possible to raise monoclonal antibodies against predefined antigens, has rendered passive immunotherapy more attractive. It is suggested that the combination of nonspecific cellular immune reactions with monoclonal antibodies may be a highly efficient antineoplastic therapy for minimal residual disease. (Author abstract) (19 Refs)

34. NUTRITIONAL ASSESSMENT OF THE CHILD WITH CANCER.

Neumann CG, Jelliffe DB, Zerfas AJ, Jelliffe EF
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Cancer Res; 42(2,Suppl):699S-712S 1982

Children with cancer are in need of nutritional support to combat the catabolic effects of malignant tumors and debilitation from surgical or other treatment and complicating infections and to maintain their immune system and other host defenses to combat cancer and infection. Also, growth must be supported in the child. Nutritional assessment should be an integral part of the care of both the hospitalized and ambulatory child. The main components of nutritional assessment are described: medical history; psychocultural history; dietary assessment; clinical examination for signs of deficiency; anthropometry; and biochemical and hematological assessment. Parameters of cell-mediated immunity, often depressed by malnutrition, are also part of the assessment. Appropriate reference data for children are included. Assessment is the first step in nutritional support. (Author abstract) (46 Refs)

35. STIMULATION BY CLL CELLS IN MIXED LYMPHOCYTE CULTURE (MLC).

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Br J Cancer; 44(5):675-681 1981

Cells from patients with chronic lymphocytic leukemia (CLL) do not respond in the mixed lymphocyte culture (MLC) but are able to stimulate the response of normal lymphocytes. Mixed lympho cyte cultures were performed using cells from 24 patients with CLL and cells from 16 normal donors. The stimulatory capacity of eight of these CLL cells was reduced when a common DR antigen was shared with the normal responding cell. We suggest that cells from certain selected CLL patients may be used in the mixed-lymphocyte reaction for determining the D-locus specificity of normal donors. CLL cells which expressed one DR antigen only, induced more clearly defined typing responses than cells with two DR antigens. There was no correlation between the ability of a CLL cell to induce a typing response and the T-cell status of the patient. However, a correlation with clinical course was suggested, because most cells which induced a typing response were obtained from patients who had received intensive treatment for the disease. (Author abstract) (21 Refs)

36. SEROLOGICAL AND FUNCTIONAL CHARACTERIZATION OF HUMAN T CELL SUBSETS.

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Clin Exp Immunol; 43(2):319-328 1981

Two specific rabbit sera against human T cells, one raised against fetal thymocytes (anti-HTY) and one raised against human cultured T cells (anti-CTC), were studied. Antisera were produced by injecting New Zealand white rabbits with fetal thymocytes or with T cells cultured in the presence of conditioned medium from peripheral blood mononuclear lymphocytes (PBL) stimulated by phytohemagglutinin. After a series of absorptions by a variety of neoplastic hemopoietic cell lines, anti-HTY and anti-CTC each showed cytotoxicity against T cells but not against B cells or null cells. In fluorescence-activated cell-sorter analyses, T cells showed a higher fluorescence intensity with the antisera than did B cells. After absorption with T chronic lymphocytic leukemia (T-CLL) cells, anti-HTY was active against thymocytes, with 40-50% of normal T-PBL, and with T cells whose rosette-forming capacity with sheep RBC was not inhibited by theophylline. PBL remaining after preincubation with anti-HTY and complement showed reduced sensitivity to stimulation by lectin or mixed lymphocyte culture (MLC), but were responsive to tetanus toxoid (t tox) After absorption with MOLT-4 cells, anti-CTC was active against 30% of T-PBL and most T-CLL cells with Fc receptors. PBL remaining after preincubation with this adsorbed serum showed enhanced sensitivity to stimulation by lectin, t tox, and MLC. Results demonstrate the existence of two distinct major subpopulations of human T cells. (33 Refs)

37. ENUMERATION OF LYMPHOCYTES AND THEIR SUBPOPULATIONS IDENTIFIED BY BACTERIAL ADHERENCE IN BLOOD SMEARS OF PATIENTS WITH BREAST TUMORS.

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J Surg Oncol; 18(4):323-329 1981

Peripheral blood lymphocyte counts were determined in 57 breast clinic patients. These patients were grouped into four clinical/pathological groups: 18 had benign breast disease, 13 had a history of breast cancer but were free of disease at the time of the study, 7 had a history of breast cancer and were free of disease at the time of the study but were on adjuvant chemotherapy, and 19 had active metastatic breast cancer. Two parameters were investigated in a double blind study: (1) the absolute lymphocyte counts and (2) the percentages of lymphocytes that bound different bacteria as markers of lymphocyte subpopulations in conventionally stained blood smears. A significant reduction in mean lymphocyte counts was demonstrated in patients with advanced disease. A significant increase in these counts was found in patients who were free of disease following surgical treatment alone. The T1 T2 cells (our denomination), the subpopulation of cells responsible for specific killing in vitro and for suppression of natural cytotoxic cells, was significantly reduced in patients with advanced disease under treatment. The T/B cell ratio in all groups was the same and within normal range. These observations suggest that the observed decrease in the total lymphocytes is due not only to an overall decrease in all classes of lymphocytes but especially in those responsible for specific cell-mediated reactions. They also show that bacteria can be used as reliable reagents for the identification of lymphocyte subpopulations in blood smears. (Author abstract) (21 Refs)

38. IMMUNOLOGIC PARAMETERS OF CHILDREN WITH ACUTE LEUKOSIS AFTER CESSATION OF POLYCHEMOTHERAPY UNDER REPEATED IMMUNOSTIMULATION WITH INTRADERMAL B.C.G.

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Arch Geschwulstforsch; 52(2):123-128 1982

Immunologic parameters were measured in children with acute leukosis during immunostimulation with BCG after cessation of polychemotherapy. Fourteen patients, including 11 with acute lymphoblastic leukemia (ALL) and 3 with acute myeloblastic leukemia (AML) began immunostimulant therapy 6 wk after cessation of a 3-yr course of intensive polychemotherapy. BCG (0.05 ml) was injected id 2x/yr up to 5 yr and once/yr thereafter. BCG vaccination produced significant increases in peripheral-blood counts of lymphocytes (4,466 x 10(9)/liter before BCG vaccination to 7,240 x 10(9)/liter 6 wk after the third vaccination) and cells forming E-rosettes (48.5 +-21.1% before BCG treatment to 53.2 +-13.0% 6 wk after the third vaccination). Three out of 24 skin tests showed positive tuberculin reaction. A control group of patients with AML who received polychemotherapy but no BCG treatments showed no such increases. No relapse occurred in 14 patients receiving BCG during 1-3 yr observation. Among controls 19/30 were alive and 15/30 were in stable remission after an av 4 yr. Results suggest beneficial effects of BCG vaccination for patients with ALL or AML, but the patient sample was too small too draw definite conclusions. (11 Refs)

39. STUDIES ON CELL-MEDIATED IMMUNITY IN PATIENTS WITH COLORECTAL CANCER: LEUKOCYTE MIGRATION INHIBITION TEST (LMIT) USING ALLOGENEIC 3 M KCL EXTRACTS.

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Kyoto Furitsu Ika Daigaku Zasshi; 90(6):473-483 1981

The cellular immune response to tumor-associated antigens (TAA) had been monitored in patients with malignant tumors. In the present study, WBC from patients with colorectal and other malignant and nonmalignant gastrointestinal diseases and from normal subjects were tested by the LMIT, utilizing five different allogeneic 3 M KCl soluble extracts of colorectal cancer tissues. The normal range of the migration index (MI) was found to be 0.82 to 1.20 by calculating the mean MI +-2 SD (standard deviation) of 10 normal subjects. MIs out of this range were considered to be pathologic. In the LMIT with a single tumor extract, pathologic MI was found in 49.3% of 71 colorectal cancer patients, significantly higher than the 12-15% of other patients. In the panel method, ie testing each blood sample with five different tumor extracts, 78.9% of the patients with colorectal cancer were reactive, while 15% of gastric cancer patients showed positive reactions and no reactivity was observed in another group of patients. The difference between the colorectal cancer patients and the other patients was statistically significant. The frequency of positive reactivity was not related to the carcinoembryonic antigen value in the extracts. Markedly depressed reactivity was seen 10-14 days after curative resection, and in patients without recurrence the MI was normal during the 1-2 mo after surgery. However, positive reactions recurred in patients with local recurrence. Thus, the LMIT, particularly when tested by a panel method, seems to detect cell-mediated immunity against TAA of colorectal cancer. (28 Refs) (In JPN)

40. MEASUREMENT OF MITOGEN-RESPONDING LYMPHOCYTES IN CANCER PATIENTS AND HEALTHY DONORS (MEETING ABSTRACT).

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VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

A study of subpopulations of human peripheral blood lymphocytes which respond to mitogenic stimulation was conducted using a modification of methodology previously reported by Udkoff et al. The conditions for recognizing the mitogen-responding lymphocytes were chosen to maximize the response of lymphocytes from healthy donors and not necessarily to maximize the possible difference between lymphocytes from healthy donors and cancer patients. Fluorescein fluorescence intensity and polarization measurements were performed on a flow cytometer. Responding subpopulations generally appeared as a second peak of lower polarization and higher intensity. Numerical curve subtraction and area integration techniques were used on the bimodal data distributions in order to estimate the number of responding lymphocytes. The data from 27 cancer patients, 2 anemia patients and 21 healthy donors show the av number of responding lymphocytes to be 25-30%. This number appeared consistent regardless of the disease, stage of disease, previous or current disease therapy, age, or sex of the donor. Moreover, a difference between number of responding lymphocytes in cancer patients and healthy donors could not be discerned with our methodology or data analysis techniques. (no Refs)

41. ROLE OF ANTIBODY IN CYTOTOXICITY BY LYMPHOCYTES ARMED AGAINST 253J BLADDER CANCER LINE.

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Int Arch Allergy Appl Immunol; 66(3):259-266 1981

The role of antibody-dependent cell-mediated cytotoxicity (ADCC) in cytotoxicity mediated by antibody-armed effector cells was examined. Cytotoxicity mediated by unsensitized human peripheral blood mononuclear cells (MNC) directed against the human bladder cancer cell line, 253J, was significantly enhanced when MNC were preincubated with a rabbit anti-253J serum and then washed free of unbound antibody. Non-adherent, Fc receptor positive MNC were the effector cells and the arming antibody was IgG. Supernatants of 24-hr cultures and armed MNC exhibited antibody activity in ADCC assays, suggesting the ADCC was in part responsible for the arming phenomenon. (Author abstract) (23 Refs)

42. HUMAN ADENOSINE DEAMINASE. PROPERTIES AND TURNOVER IN CULTURED T AND B LYMPHOBLASTS.

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J Biol Chem; 256(23):12496-12501 1981

Changes in the level of adenosine deaminase activity have been associated with normal T cell differentiation and T cell diseases, such as acute lymphoblastic leukemia; however, possible mechanisms controlling the level of this enzyme have not been explored. In this study, the properties and rate of turnover of adenosine deaminase are compared in cultured human T and B lymphoblast cell lines. Relative to B lymphoblasts, the level of adenosine deaminase activity in extracts of T lymphoblast cell lines is elevated 7-14-fold and differs by two-fold between the T cell lines. In both T and B lymphoblast extracts, the enzyme is apparently identical, based on Km for adenosine and deoxyadenosine, Ki for inosine, Vmax for adenosine, s20,w, isoelectric pH, and heat stability. Furthermore, by radioimmunoassay, the quantity of adenosine deaminase-immunoreactive protein is proportional to the level of enzyme activity in all cell lines studied. Using a purification and selective immunoprecipitation technique, the enzyme turnover could be assessed in cell lines labeled with [35S]methionine. The apparent rate of adenosine deaminase synthesis, relative to total protein, is two-fold faster in T cell lines than in the B cell lines studied. The apparent half-life (t1/2) for the enzyme degradation is 19-39 hr, respectively, in T cell lines while the t1/2 in both B cell lines is 7-9 hr. From the net rate of synthesis and degradation, the T cell lines, respectively, exhibit approximately a 6-and 12-fold difference in adenosine deaminase turnover relative to B cells, consistent with the observed differences in enzyme activity. This study suggests that while adenosine deaminase is apparently identical in both T and B lymphoblast cell lines, alterations in both the rate of enzyme synthesis and degradation contribute to its high steady state level in T cells. (38 Refs)

43. THE IN VITRO EFFECT OF A CALF THYMUS EXTRACT (THYMOSTIMULIN) ON THE IMMUNOLOGIC PARAMETERS OF PATIENTS WITH UNTREATED HODGKIN'S DISEASE.

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Cancer; 49(2):245-250 1982

The in vitro effect of a calf thymus extract, thymostimulin (TP-1), on the E-rosette-forming capacity and on the PHA blastogenic response of peripheral blood lymphocytes was evaluated in 20 patients with untreated Hodgkin's disease. The mean percentage of lymphocytes forming E rosettes increased in patients from 44.2% to 57.5% (p less than 0.005). The mean PHA stimulation index rose with all three concentrations tested, but returned to the normal range only with the highest PHA concentration (60 u/ml). An increase in the immune parameters was greatest in those patients who presented with decreased E-rosetting cells or total lymphocyte counts or whose disease was Stage III or IV or of mixed cellular histology. (Author abstract) (30 Refs)

44. CELL-MEDIATED IMMUNITY IN BREAST CANCER PATIENTS IN RELATION TO CLINICAL STAGES.

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Cell Mol Biol; 27(5):551-556 1981

Cell-mediated immunity of patients with breast cancer at clinical stage I, II, I II or IV, prior to any therapy, was evaluated in relation to their clinical stage. In vitro peripheral blood studies included: absolute number of lymphocytes/ul; absolute number of T-lymphocytes/ul (E-rosette-forming cells); lymphocytes' response to phytohemagglutinin. In vivo assays consisted of delayed hypersensitivity skin tests to ubiquitous antigens and 2,4-dinitrochlorobenzene sensitization. The results obtained can be summarized as follows: absolute numbers of total lymphocytes/ul were lower in breast cancer patients than in the normal group. However, the values corresponding to Stage IV were the only ones significantly different when compared with normal and with any other clinical stage. Absolute numbers of T-lymphocytes/ul were lower in breast cancer patients than in the normal group, and statistically significant differences were found when Stages II, III or IV were each compared with the normal group. Furthermore, a significant decrease in the number of T-lymphocytes was observed in Stage IV, as compared with any other clinical stage. Transformation indices obtained from lymphocyte cultures of patients were lower than those observed in normals. However, the values corresponding to Stage I were the only ones significantly different. Moreover, the transformation index of Stage I was also significantly lower than that of Stage IV. The percentages of positive skin tests to purified protein derivative were significantly lower in Stage II, III or IV than in either Stage I or the normal group. The percentage of positive skin tests to Candida albicans antigen was significantly decreased in Stage IV. Finally, the percentages of positivity to 2,4-dinitrochlorobenzene sensitization were lower in all clinical stages of breast cancer than in the normal group. In Stage II, immune competence was not affected by metastatic involvement of regional lymph nodes. The observed differences cannot be attributed to age. (Author abstract) (27 Refs)

45. DEPRESSED CELLULAR IMMUNITY IN HEPATOCELLULAR CARCINOMA PATIENTS.

Lee CS, Chang KJ, Lin TY, Hsieh KH, Tung TC
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Taiwan I Hsueh Hui Tsa Chih; 80(8):780-785 1981

The techniques of sheep RBC rosette formation (E rosettes) and sheep RBC-antibody-complement formation (EAC rosettes) were used to study lymphocyte subpopulations in 40 patients with hepatocellular carcinoma (HCC) and in 120 age- and sex-matched normal controls. In the peripheral blood, E rosette-forming T cells comprised 49.18 +-10.92% of the lymphocytes from HCC patients compared to 72.00 +-11.50% in controls (p less than 0.001). EAC rosette B cells comprised 24.0% of the lymphocytes in both groups. The mitogenic index in the phytohemagglutinin-stimulated lymphocytes of 20 HCC patients was 12.26 +-17.82 (range 0.80-35.40) compared to 83.00 +-21.70 (range 18.00-124.80) in 40 controls. Serum alpha-fetoprotein (AFP) was determined in the 40 HCC patients. In the 28 with positive response, T cell count was 50.68 +-10.40% compared to 45.67 +-12.31% in 12 with negative response. The difference was not significant. Among 20 HCC patients tested for lymphocyte transformation, serum AFP was positive in 13 and negative in 7; mitogenic indices were 16.39 +-20.77 and 4.59 +-6.11, respectively. The difference was not significant. The significance of the low T cell count in peripheral blood of HCC patients is discussed. (16 Refs)

46. CELL-MEDIATED IMMUNITY IN EARLY PREGNANCY AND TROPHOBLASTIC NEOPLASIA (MEETING ABSTRACT).

Oh WS, Song SK, Cho BC, Kim SJ
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Obstetrics and Gynaecology: 8th Asian Congress, October 25-31, 1981, Melbourne, Australia. Asia and Oceania Federation of Obstetricians and Gynaecologists 352 pp., 1981.

Cell-mediated immunity studies were carried out serially in 20 healthy women, 27 healthy pregnant women and 134 patients with gestational trophoblastic neoplasia (GTN). The authors employed a battery of lymphocyte monitoring techniques: absolute lymphocyte counts, dinitrochlorobenzene (DNCB) skin testings, phytohemagglutinin (PHA) induced lymphocyte transformation and T-lymphocyte rosettes. Women with early gestation and patients with GTN stage O revealed a significant decrease in DNCM skin reaction, 3H-thymidine uptake of PHA-stimulated lymphocytes and the proportion of peripheral lymphocytes as compared with the healthy non-pregnant controls. Patients with GTN stage I-IV revealed a significant reduction of total lymphocyte count, DNCB reactivity, rosette formation and 3H-thymidine uptake of PHA-stimulated lymphocytes, especially in advanced stages. Patients with initially low cell-mediated immunity exhibited poor responses to the anti-cancer chemotherapy. Autologous serum added to lymphocyte transformation in early pregnancy and trophoblastic neoplasia, but not in healthy non-pregnant controls. It is postulated this decreased cell-mediated immunity of pregnant women and GTN is due to human chorionic gonadotropin. (no Refs)

47. HUMORAL AND CELLULAR NON-SPECIFIC IMMUNE RESPONSE IN UNTREATED HODGKIN- AND CERVICAL CARCINOMA PATIENTS (MEETING ABSTRACT).

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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

In 58 patients with grade I-IV Hodgkin's disease, histologic type LP, NS, MC or LD and in 50 patients ill of cervical carcinoma grade II the blood levels of IgA, IgM and IgG, the immunelectrophoretic pattern of serum proteins, the absolute lymphocyte count, the per cent proportion of lymphocytes B (surface immunofluorescence) and T (SE-rosettes), the degree of blastic transformation (with phytohemagglutinin) and the activity of LT-factor(lymphotoxin - method of Spofford et a) were determined. Moreover, in Hodgkin patients the skin test with dinitrochlorobenzene (method of Catalona et al) was performed. In all patients the levels of IgA, IgM and IgG were increased. Also the appearance of increased orosomucoid, ceruloplasmin, transferrin, or haptoglobins, sometimes of paraproteins could be observed. The percentage of B lymphocytes was in Ccu patients higher than in controls, on the contrary it was lower in Hodgkin patients. In both diseases the percentage of T lymphocytes was lowered with a simultaneous relative increase in the production of the LT-factor. The degree of blastic transformation falls down in all patients. With help of the Mantel-Henszel's test for survivorship data a positive correlation between the LT-activity before treatment and prognosis was established in Ccu patients. In the group of Hodgkin patients which was less homogenous as far as sex age and clinical stage are concerned, such a correlation could not be confirmed. (no Refs)

48. IDENTIFICATION OF GOOD AND BAD PROGNOSTIC GROUPS IN LUNG AND BREAST CANCERS THROUGH PREOPERATIVE EVALUATION OF MACROPHAGE CHEMOTAXIS (20 MONTHS MEDIAN FOLLOW-UP) (MEETING ABSTRACT).

Samak R, Israel L, Grefft-Alami A
No affiliation given
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

A modified version of the skin window technique consisting of a superficial skin abrasion and serially applied coverslips to collect adherent cells was used to study in vivo non-specific macrophage migration in 180 patients with stage I and stage II lung and breast cancer. Preoperatively the number of macrophages migrating between 12 and 24 hr correlated closely with lymph node status as determined by pathologic examination after operation. Patients without lymph node involvement (N-) showed a significantly stronger response than controls whereas those with lymph node involvement (N+) had a diminished response compared to controls. Median follow-up of these preoperatively tested patients is now more than 2 yr (2+ to 42+ mo). Correlations between the macrophage response and disease-free survival revealed the following findings: Among N+ patients, who generally exhibited poor macrophage migration capacity, about 15% had a strikingly better response than the group as a whole. These patients also had a much longer disease- free survival than the other 85% and generally had only one involved lymph node. Among the N- patients, who generally showed stronger macrophage migration capacity than controls, about 20% had a strikingly weaker response than the rest of the group and an unusually poor prognosis. This simple and reproducible test allows preoperative detection of patients who, despite their lack of lymph node involvement, have a very poor prognosis in terms of disease-free survival. (no Refs)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

49. ENHANCEMENT BY IMMUNOSTIMULANTS OF THE PRODUCTION BY MOUSE SPLEEN CELLS OF FACTOR(S) STIMULATING DIFFERENTIATION OF MOUSE MYELOID LEUKEMIC CELLS.

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Gan; 72(6):828-833 1981

Mouse myeloid leukemic Ml cells can be induced to differentiate into macrophages and granulocytes in vitro by a factor(s) stimulating differentiation of the cells (D-factor) or by various chemical compounds. Spleen lymphocytes and spleen macrophages have been shown to produce D-factor when treated with various mitogens including lipopolysaccharide or synthetic double-stranded polyribonucleotide, poly(I).poly(C). Several immunostimulants from microorganisms were tested for ability to induce differentiation of Ml cells and to stimulate production of D-factor by spleen cells. Mycobacterium bovis BCG (500 ug/ml) and the cell wall skeleton of Nocardia rubra (50 ug/ml) induced differentiation of Ml cells, but Corynebacterium parvum CN6134 and the cell wall skeleton of Propionibacterium acnes C7 had no effect on Ml cells. On the other hand, all immunostimulants tested at concentrations of more than 10 ug/ml were found to stimulate production of D-factor by both spleen lymphocytes and spleen macrophages. Synthetic derivatives of N-acetylmuramyl dipeptide (MDP), the minimal adjuvant-active subunit of the bacterial cell wall, had no direct effect on the differentiation of Ml cells and only slightly stimulated the production of D-factor by spleen cells. Therefore, the structure of microorganisms required for induction of differentiation of Ml cells and for stimulation of production of D-factor are suggested to be different from that of MDP. (Author abstract) (27 Refs)

50. ASSOCIATION OF IMPAIRED IMMUNE RESPONSIVENESS OF LYMPHOCYTES FROM ANIMALS BEARING LARGE TUMORS WITH A MEMBRANE-BOUND SUPPRESSIVE SUBSTANCE.

Wang BS, Heacock EH, Onikul SR, Chang-xue Z, Young TH, Mannick JA
Chemotherapy Res. Dept., Lederle Lab., The American Cyanamid Co., Pearl River, NY, 10965
Cancer Res; 42(2):416-420 1982

The immunoreactivity of lymphocytes from mice bearing large tumors was investigated. As compared to normal lymphocytes, lymphocytes from tumor bearers manifested a lessened proliferative response to T-cell mitogens and were less capable of destroying syngeneic tumor target cells. However, the impaired reactivity of these lymphocytes was improved significantly after washing repeatedly in tissue cultur e medium in vitro. The increase in cytolytic activity was tumor specific. A membrane-associated suppressive substance was detected in the washing medium which inhibited the cytotoxicity of washed lymphocytes. The effect of suppressive substance was tumor specific and sensitive to treatment with protein A and anti-immunoglobulin antibody, indicating that the suppressive substance contained immunoglobulin. The present findings suggest that a membrane-associated suppressive substance(s) may be in part responsible for the diminished immune responsiveness of lymphocytes from animals bearing large tumors. (Author abstract) (23 Refs)

51. THE EFFECT OF LOCAL TUMOR IRRADIATION ON CELL-MEDIATED TUMOR IMMUNITY IN TUMOR-BEARING MICE.

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Dept. Radiology, Jikei Univ. Sch. Medicine, Jikei, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(9):887-893 1981

The effect of inoculation of spleen lymphocytes derived from tumor-bearing mice irradiated locally to tumor on the ability to suppress tumor incidences of syngeneic mice was studied on sarcoma to be grown in the leg of BALB/c mice using Winn assay. The tumor-specific cytotoxicity of spleen lymphocytes was most distinct when the spleen lymphocytes taken out on the 7th day after irradiation with the dose of 1,000 rad or more from the tumor-bearing mice locally irradiated on tumors of the size of 8 mm in diameter was given, and even when the 15 mm diameter's tumor was used, the cytotoxicity of spleen lymphocytes was activated after x-irradiation of the tumor. Suppression of tumor incidence was clearer in the group inoculated tumor cells and lymphocytes in the ratio of 1:200 compared with the ratio 1:50. These results suggest that tumor specific immunopotential can be obtained by local x-irradiation to tumors. (Author abstract) (26 Refs) (In JPN)

52. MEASUREMENT OF ANTITUMOR AND ADJUVANT EFFECTS OF INTERFERON WITH TRANSPLANTABLE AND OTHER TUMORS IN MICE.

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Methods Enzymol; 79:414-419 1981

The effects of interferon (IF) on experimental mammary adenocarcinoma (MAC) line 16/C and leukemia (MBL-2) cells are described, with emphasis on the cytoreductive effect of IF. Response of MAC to IF and IF inducers was determined in four groups of B6C3F1 female mice inoculated sc with 1 x 10(7) 16/C cells treated as follows: phosphate-buffered saline (control), IF (100,000 units), Pyran (MVE-6: 8 mg/kg), or BruPel (8 mg/kg). Intralesional treatments (id injections around the the tumor site) were given starting on day 3 and continued daily for 18 days. Tumor sizes were greatest in the control mice, followed by those treated with IF, MVE-6, and BruPel. Mean survival times (in days) were 24, 40, 55, and 40, respectively. In the assay of in vivo antitumor activity, MBL-2 leukemic ascites cells were inoculated ip in C 57/BL/6 male mice and groups were treated with a test agent starting on day 1 and continued daily for 5 days: bovine serum albumin (BSA, 0.5 mg), IP (100,000 units), or MVE-6 (0.2 mg). Each group was divided into mice used to determine tumor-induced death rates and those sacrificed (at day 6) to provide macrophages for use against fresh MBL-2 cells. The in vivo evaluation yielded the following mean survival times in days: control, 18; BSA, 23; IF, 38; and MVE-6, 48. In vitro tumor cell deaths (percent) were: BSA, 25; IF, 52; and MVE-6, 80. Macrophages harvested from these treated groups, and incubated in vitro with freshly prepared MBL-2 tumor cells, had a significantly greater tumoricidal effect than those from the placebo-treated group. It is suggested that the IF antiproliferative effect on tumor cells may be a direct effect, or an enhancement of cellular immune responses by direct activation of natural macrophage and natural killer cell tumoricidal activity. (16 Refs)

53. INCREASED RESPONSES TO LYMPHOKINES ARE CORRELATED WITH PRELEUKEMIA IN MICE INOCULATED WITH MOLONEY LEUKEMIA VIRUS.

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Proc Natl Acad Sci USA; 78(12):7712-7716 1981

In various mouse strains, inoculation with Moloney leukemia virus results in the establishment of an acute viremia which in most cases is followed by the induction of leukemia. Also associated with the viremia is the development of a chronic cellular immune response detectable in vitro by the ability of viral proteins to induce splenic lymphocyte proliferation. Previous studies have demonstrated that, in the absence of this cellular immune response, leukemia does not develop irrespective of whether viremia is present. In vitro proliferative responses to antigens involve the nonspecific response of various subpopulations of lymphocytes to lymphokines produced by antigen-specific Thy 1+, Lyt 1+,2-lymphocytes. The studies presented here concern the effects of a chronic immune response in viremic mice on the frequency of lymphocytes capable of responding to lymphokines in vitro. The data demonstrate that the number of responsive lymphocytes is increased 30-to 100-fold in preleukemic mice and that such increases are dependent upon the induction of an immune response in viremic mice. The role of this altered immune response in leukemia is discussed. (Author abstract) (18 Refs)

54. MHC-CODED UNIQUE ALLOANTIGENS AND ANTITUMOR IMMUNITY.

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Transplant Proc; 13(4):1837-1840 1981

Evidence for the role of H-2K-region-coded unique determinants distinguishing C3H/HeN mice (C3H) and C3HfB/HeN mice (C3Hf) in antitumor immunity is reviewed. Differences between the two strains of mice were confirmed by analyzing the specificity of cytotoxic T lymphocytes (CTL) derived from reciprocal mixed lymphocyte reaction (MLR). C3Hf anti-C3H MLR-derived CTL cross-react only with target cells of H-2Kk haplotype; C3H anti-C3Hf MLR-generated CTL are specific for C3Hf-derived target cells and do not cross-react with cells from other mouse strains. Characterization of the two types of cytotoxic cells reactive with the k-unique antigen obtainable in MLR using C3Hf responding cells and either C3H or B10 stimulating cells gave results similar to those found with stimulation of C3Hf spleen cells with cells from several other allogeneic mouse strains. Conventional CTL and natural killer-like cytotoxic cells can apparently be generated against unique alloantigens. The C3Hf:C3H model is a convenient system to analyze expression and immunogenicity of the k-unique antigen in tumors of mice of H-2k haplotype. The model also provides convincing evidence for a novel type of tumor-associated alteration in H-2 antigen expression. (10 Refs)

55. NATURAL KILLER ACTIVITY OF GUT MUCOSAL LYMPHOID CELLS IN MICE.

Tagliabue A, Luini W, Soldateschi D, Boraschi D
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Eur J Immunol; 11(11):919-922 1981

Intraepithelial lymphoid cells (IEL) obtained from the mucosa of mouse small intestine were tested for natural killer (NK) activity in a 20-hr 51Cr-release assay against YAC-1 and RL male 1 tumor cells. It was found that IEL possess a strong NK activity, higher than spleen cells, whereas lymphocytes from Peyer's patches (PPL) did not show any NK activity. The cytotoxic activity of IEL could be boosted by interferon (IFN-beta) treatment, but no NK activity could be induced in PPL by in vitro IFN-beta treatment. The characteristics of the NK effector cells present in the mouse intestine strictly resemble those of NK cells in the spleen. In fact, intestinal NK activity is not affected by depletion of adherent cells and only partially reduced by anti-Thy-1.2 antibodies plus complement. Moreover, the age dependency of NK cytotoxicity is identical for IEL and spleen. Finally, NK-insensitive target cells are not lysed by IEL. (Author abstract) (17 Refs)

56. STUDIES OF TUMOR-SPECIFIC CELLULAR IMMUNE RESPONSES WITH SOLUBLE TUMOR ANTIGEN IN MICE. I. IMMUNOGENICITY OF HYPOTONIC SALINE EXTRACTS OF TUMOR CELLS.

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Nippon Geka Gakkai Zasshi; 82(6):566-574 1981

There are several assay methods to demonstrate cell-mediated immunity to the tumor of cancer patients. In these assays, usually whole tumor cells have been used as targets or immunogens for tumor sensitization. Suitable cell suspensions or cultures are rather difficult to prepare from the s olid tumors. In order to prepare experimentally stable antigenic extracts easily, a soluble tumor antigen was prepared from mouse ascites hepatoma cells by a hypotonic saline extraction method. Immunogenicity of the hypotonic saline extracts was estimated by footpad assay for delayed cutaneous hypersensitivity and by lymphocyte blastogenesis to the tumor antigen (MLTR). Transplantability of the hepatoma cells was also tested in mice immunized with the soluble extract and BCG. In the footpad assay the immunized mice showed a higher response than the nonimmunized mice. In micro-MLTR studies, the optimum concentration of hypotonic saline extracts was 1.0 ug/ml and the max lymphocyte blastogenesis was observed on the 4th culture day. There was a significant relationship between the reaction in the footpad assay and the degree of lymphocyte blastogenesis. In the immunized mice, tumor-transplantation resistance and survival rate of the mice with growing tumors were higher than those in the nonimmunized mice. These results indicate that hypotonic saline extracts of tumor cells possess immunogenicity that could induce transplantation immunity when injected along with BCG. (43 Refs) (In JPN)

57. STUDIES OF TUMOR-SPECIFIC CELLULAR IMMUNE RESPONSES WITH SOLUBLE TUMOR ANTIGEN. II. KINETICS OF THE CELLULAR IMMUNE RESPONSES IN MICE WITH GROWING TUMORS.

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Nippon Geka Gakkai Zasshi; 82(7):693-701 1981

Measurement of cell-mediated immunity, specific and nonspecific, is important in estimating the prognosis and clinical state of cancer patients. In order to see what kinds of assays for cell-mediated immunity reflect the immunological state of cancer patients, kinetics of the cellular immune responses in C3H/He mice with growing MH134 tumors was carried out by the footpad assay, lymphocyte blastogenic response to a soluble tumor antigen (MLTR), leukocyte migration inhibition test (LMIT) using a soluble tumor antigen and lymphocyte blastogenic response to phytohemagglutinin (PHA) and concanavalin A (Con A). Soluble tumor antigens were prepared from MH134 cells by the hypotonic saline extraction method. These assays were carried out 0, 6, 8, 10, 13, 16 and 21 days after sc transplantation of MH134 cells. Footpad, MLTR and LMIT responses reached their max 10 days after tumor transplantation, and then decreased along with progressive tumor growth. The lymphocyte-blastogenic response to PHA reached a peak on day 6, Con A on day 8, and then both declined. A correlation between tumor diameter and PHA response was observed. An interesting significant relationship between the in vivo footpad reaction and the in vitro lymphocyte blastogenic responses to the tumor antigen and Con A was demonstrated. These results suggest that the measurement of immunological status with the use of a soluble tumor antigen might be useful for the study of specific immune responses in cancer patients. (17 Refs) (In JPN)

58. MEASUREMENT OF THE RATE OF DEATH OF DOG TUMOUR CELLS TRANSPLANTED INTO ATHYMIC 'NUDE' MICE.

Holmes JM
Sub-Dept. Veterinary Anatomy, Tennis Court Road, Cambridge, England
J Comp Pathol; 91(4):511-519 1981

The rate of death of canine tumor cells xenografted ip or sc into athymic nude mice was measured using a 125I-deoxyuridine technique. No evidence was found for a specific cell-mediated immune response which could be reduced by irradiation or stimulated by prior exposure to osteosarcoma cell antigens. (15 Refs)

59. IMMUNOSUPPRESSION ASSOCIATED WITH SJL/J MURINE LYMPHOMA. I. SUPPRESSION OF CELL-MEDIATED IMMUNE RESPONSES AFTER TUMOR TRANSPLANTATION.

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JNCI; 67(6):1269-1275 1981

The proliferative responses of peripheral blood lymphocytes of inbred SJL/J mice to the mitogens phytohemagglutinin and concanavalin A were evaluated serially in individual animals before and after induction of lymphomas by transplantation. Tumor-bearing mice exhibited marked suppression of mitogen responsiveness. Proliferative responses in mixed lymphocyte-tumor cell culture and mixed lymphocyte culture were also suppressed. Suppression of responses was tumor related, and responsiveness was restored in animals whose tumors regressed. There was no deficiency of responder T-cells in the peripheral blood of tumor-bearing animals, and suppressor cell activity was not demonstrable in a number of in vitro assays. However plasma from tumor-bearing animals exhibited potent immunosuppressive activity. The presence of plasma suppressive activity was similarly tumor related. Thus this study demonstrates nonspecific suppression of cell-mediated immune responses following tumor induction, apparently mediated by a plasma suppressor factor. (Author abstract) (35 Refs)

60. CONCOMITANT PRESENCE OF ANTI-TUMOR EFFECTOR CELLS AND SUPPRESSOR CELLS IN THE SPLEEN OF TUMOR-BEARING MICE: THE NATURE OF SUPPRESSOR CELLS.

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Dept. Surgery, Okayama Univ. Medical Sch., Okayama 700, Japan
Acta Med Okayama; 35(4):247-261 1981

In order to investigate the immunological responsiveness of tumor-bearing hosts to tumor cells, splenic suppressor cells from Ehrlich tumor-bearing mice that inhibited anti-tumor effector cell activity were characterized. In vitro cell-mediated cytotoxicity and cytostasis assays were performed to test for the existence of anti-tumor immunity. Suppressive activity assayed by cell mixture experiments became apparent with decline of anti-tumor immunity and progressive tumor growth. The cells mediating the suppression were found to be nylon wool column adherent T cells and inhibited T cell dependent cytotoxicity rather than non-T cell dependent cytostasis. In vivo cell transfer experiments demonstrated that intravenous injection of suppressor cells to a host already inoculated with tumor cells mixed with antitumor effector cells resulted in significant enhancement of tumor growth. This inhibition of in vivo neutralization assay by suppressor cells was found in not only allogeneic but also syngeneic tumor system. Splenectomy at the time of tumor resection endowed the host with stronger resistance against subsequent reinoculated tumor than sham-splenectomy did, reflected by prolonged survival times. These results suggest that splenectomy combined with surgical removal of the tumor is a useful treatment of clinical malignancies. (Author abstract) (37 Refs)

61. SUSCEPTIBILITY OF VARIOUS STRAINS OF MICE TO URETHAN-INDUCED LUNG TUMORS AND DEPRESSED NATURAL KILLER CELL ACTIVITY.

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JNCI; 67(6):1317-1322 1981

Inbred A/J, CBA/J, and C57BL/6 mice at age 7-8 wk were inoculated with 1 mg urethan/g body wt. Three mo later, 13.2, 1.8, and 0.1 tumors per lung were found in these mice, respectively. Cytotoxicity by spleen cells of normal and urethan-treated mice was analyzed in a 4-hr 51Cr release assay against YAC-1 cells. During the first 2 wk after treatment, urethan strongly suppressed the cytotoxicity by spleen cells of A/J mice but had relatively little effect on the reactivity of spleen cells of CBA/J mice. Natural killer (NK) activity was not suppressed in urethan-treated C57BL/6 mice. The effect of urethan on natural in vivo antitumor resistance in the lungs was studied by measurement of elimination from the lungs of [125I]deoxyuridine-labeled YAC-1 cells. Urethan caused profound and sustained suppression of in vivo NK reactivity in the lungs of A/J mice, had only a transient effect on CBA/J mice, and had no detectable effect on C57BL/6 mice. The differences in the effects of urethan on the natural antitumor resistance in the three strains of mice could not be attributed to a generally greater susceptibility of A/J mice to inhibition of NK activity, since cyclophosphamide (0.15 mg/g) equally suppressed the clearance from the lungs of the radiolabeled tumor cells in A/J, CBA/J, and C57BL/6 mice. These results indicate a positive correlation between susceptibility of A/J, CBA/J, and C57BL/6 mice to urethan-induced lung carcinogenesis and inhibition of in vitro and in vivo natural cell-mediated cytotoxicities and support the hypothesis that NK cells play a role in resistance to urethan-induced lung carcinogenesis. (Author abstract) (24 Refs)

62. LOW-DOSE CYCLOPHOSPHAMIDE INHIBITION OF TRANSPLANTABLE FIBROSARCOMA GROWTH BY AUGMENTATION OF THE HOST IMMUNE RESPONSE.

Ray PK, Raychaudhuri S

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JNCI; 67(6):1341-1345 1981

Preinjection of a low dose of cyclophosphamide (Cy) (500 ug/mouse) either delayed or inhibited tumor appearance following the inoculation of transplantable 3-methylcholanthrene-induced fibrosarcomas in inbred male C3H/HeJ mice. This dose of Cy decreased the spleen wt by 13% and the total spleen cell count by 23%. However, the same dose could potentiate the footpad swelling reaction (FPSR) measured against Staphylococcus aureus antigen. Splenic lymphocytes from Cy-treated animals showed increased blastogenic response against phytohemagglutinin-M and bacterial lipopolysaccharide. Thus 500 ug Cy/animal may have depleted suppressor cell populations leading to: an increase in FPSR; increased blastogenic transformation of lymphocytes; and tumor growth inhibition. (Author abstract) (36 Refs)

63. SUPPRESSION OF CONTACT HYPERSENSITIVITY BY UV RADIATION AND ITS RELATIONSHIP TO UV-INDUCED SUPPRESSION OF TUMOR IMMUNITY.

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Photochem Photobiol; 34(6):683-689 1981

In this study, we examine some of the photobiologic and immunologic characteristics of the suppression of contact hypersensitivity (CHS) by UV radiation. BALB/c mice were irradiated on the shaved dorsal skin with FS40 sunlamps and sensitized 5 days later by applying a contact sensitizer to the shaved abdomen. The suppression of CHS resulting from exposure to a given total dose of UV radiation was unaffected by changes in dose fractionation over a 5-day period and by changes in dose-rate over a 10-fold range. Elimination of wavelengths below 315 nm with a mylar filter abrogated the suppressive effect of the sunlamps, even when the same total energy was administered. Irradiation of unshaved mice required 14 times more energy to produce 50% suppression than was required for shaved mice, suggesting that the exposed skin is the primary target of this effect. Contact sensitization of UV-irradiated, but not unirradiated, mice induced the appearance of antigen-specific suppressor T lymphocytes in their spleen. The photobiologic and immunologic similarities between the suppression of CHS by UV radiation and the UV-mediated suppression of tumor rejection that we described previously suggest that these two immunosuppressive effects of UV exposure share certain steps in their pathways. (Author abstract) (28 Refs)

64. VARIATION IN MHC ANTIGENIC PROFILES OF TUMOR CELLS AND ITS BIOLOGICAL EFFECTS.

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Immunol Rev; 60:85-127 1981

Four kinds of Gross virus leukemias were studied; long transplanted cell lines derived from spontaneous AKR mice leukemia K36 maintained and propagated both in vivo and in vitro, tumor cell line K-GV induced in female BALB/K mice, newly isolated spontaneous AKR leukemias, and tissue culture clones established from AKR spontaneous leukemias. Absence of the H-2Kk gene product from the K36 and K-GV leukemias was noted. Cellular immunological tests and immunochemical analysis performed showed that Gross virus T cell toxicity is H-2Kk restricted. There is a direct correlation between the representation of the H-2Kk product on the tumors and the ability to lyse them with T cells in vitro. Tumors with decreased or absent H-2Kk tend to grow in mice. Biological consequences of losses and gains of major histocompatibility system (MHS) were studied. It was suggested that similar to immunoglobulins more than one gene may encode individual MHS molecules. (82 Refs)

65. T-CELL LEUKEMIA INDUCED BY 1-PROPYL-1-NITROSOUREA IN FISCHER RATS.

Imamura N, Saito O, Dohy H, Ogiu T

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Experientia; 37(12):1339-1340 1981

T-cell leukemia was induced at a high rate in female Fischer rats by continuous oral administration of 1-propyl-1-nitrosourea. No association of oncorna viruses were found in the leukemogenesis. (Author abstract) (10 Refs)

66. EFFECT OF THYMECTOMY ON DEVELOPMENT OF LUCKE RENAL ADENOCARCINOMAS IN VIRUS-INFECTED LEOPARD FROG TADPOLES.

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JNCI; 68(1):133-138 1982

Thymectomy of very young leopard frog (Rana pipiens) larvae dramatically reduced in vitro lymphocyte responses to the mitogen phytohemagglutinin-P and prolonged survival of Lucke tumor alloimplants. However, tumor incidence in premetamorphic or metamorphosing frogs that had received injections as embryos of Lucke tumor herpesvirus (LTHV) was the same in thymectomized and normal immunocompetent animals. This result suggests that T-cell-mediated cytotoxicity does not prevent development of Lucke tumors in immunocompetent larvae and that if tumor-specific transplantation antigens appear, they may induce tolerance rather than destructive immunity in normal LTHV-infected larvae. (Author abstract) (37 Refs)

67. NATURAL KILLER CELL ACTIVITY IN CHICKENS EXPOSED TO MAREK'S DISEASE VIRUS: INHIBITION OF ACTIVITY IN SUSCEPTIBLE CHICKENS AND ENHANCEMENT OF ACTIVITY IN RESISTANT AND VACCINATED CHICKENS.

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Avian Dis; 25(4):882-893 1981

Disease response and natural killer (NK) cell expression was studied in specific-pathogen-free chickens of lines P and N for up to 6 wk after inoculation with the cloned preparation (111S) of Marek's disease (MD) virus (MDV). MDV was highly pathogenic for line-P chickens, while those of line N were resistant to clinical MD, but became infected after inoculation with MDV. NK cell reactivity was assayed in an in vitro cytotoxicity assay in which effector cells from the spleen of test chickens were reacted with 51Cr-labeled LSCC-RP9 target cells. After infection, line P chickens developed progressive debilitating disease and a high incidence of gross tumors and death. NK cell reactivity in these chickens was significantly lower than that of uninfected control hatchmates. NK cell levels were significantly elevated in MDV-infected line N chickens resistant to MDV and in chickens of line P or N that had been inoculated with herpesvirus of turkeys. NK cell levels were also elevated in line P if chickens were vaccinated before MDV infection. This study may indicate a role for the NK cell system in regulating resistance to MD. (29 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

68. SPECIFIC CYTOTOXICITY AGAINST AUTOLOGOUS TUMOUR AND PROLIFERATIVE RESPONSES OF HUMAN LYMPHOCYTES GROWN IN INTERLEUKIN 2.

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Int J Cancer; 29(1):33-39 1982

Peripheral blood lymphocytes of cancer patients were sensitized in vitro to autologous tumor cells in mixed lymphocyte-tumor culture (MLTC). Blast cells were isolated on discontinuous Percoll gradients from MLTC which showed significant stimulation of [3H]-thymidine incorporation. Cultured T cells (CTC) were derived from these blasts by growth in conditioned medium containing interleukin-2 (IL-2) and maintained for up to 51 days by repeated feeding with IL-2 and in some cases by addition of irradiated allogeneic blood mononuclear cells as 'fillers.' These cultures showed specific cytotoxic reactivity against autologous tumor, and in only a few cases was natural killing (NK) of K562 cells apparent. Restimulation of CTC with tumor was measured in primed lymphocyte tests (PLT). Increased uptake of [3H]-thymidine was found upon stimulation by autologous tumor and allogeneic tumor of the same site and histology, but there was no response to non-related tumors or to a panel of allogeneic lymphocytes. No sensitization to autologous HLA D/DR could be detected by restimulation or cytotoxicity against monocytes in the majority of cases. These data suggest that, by careful selection of sensitized blasts from MLTC, it is possible to obtain CTC with both helper (proliferative) and cytotoxic T cells and that such CTC have specific reactivity against tumor cells. These cellular reagents will be useful in defining the antigenicity of human neoplasms and possibly in therapy. (Author abstract) (39 Refs)

69. HELPER VIRUSES ASSOCIATED WITH AVIAN ACUTE LEUKEMIA VIRUSES INHIBIT THE CELLULAR IMMUNE RESPONSE.

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Virology; 116(1):61-71 1982

The cellular immune competence of lymphocytes obtained from birds infected with acute or chronic leukemia viruses was studied. The in vitro blastogenic response of thymus-derived lymphocytes (T cells) to the mitogens phytohemagglutinin (PHA) and concanavalin A (Con A) correlates with the ability of birds to elicit a cellular immune response. The PHA response of splenic lymphocytes from birds infected with the avian acute leukemia viruses, myelocytomatosis virus strain 29 (MC29), avian erythroblastosis virus (AEV), avian myeloblastosis virus (AMV), or reticuloendotheliosis virus (REV-T), was completely suppressed within 1 wk after virus infection. The early induction of immunosuppression is therefore a general feature of infection of chickens by avian acute leukemia viruses. Spleen cells from chickens infected with the chronic leukemia viruses, Rous-associated viruses (RAVs) Types 1 and 3, exhibited PHA responses similar to those of uninfected birds. In contrast, lymphocytes from RAV-2 infected birds had suppressed PHA responses. Acute leukemia viruses are replication-defective and are associated with replication-competent nontransforming helper viruses. When chickens were infected with helper viruses isolated from the acute leukemia virus stocks by endpoint dilution, the T-cell response to various T-cell mitogens was completely suppressed. the helper viruses, therefore, contribute to the immunosuppression which occurs during the development of avian acute leukemia. The rapid lethality of the acute leukemia virus could be, in part, the result of the immunosuppressive activity of the associated helper viruses. Though all the acute leukemia viruses severely immunosuppress their hosts, the mechanism by which the immunosuppression was induced by these viruses differed. REV-T was the only acute leukemia virus which induced a population of splenic suppressor cells. All the viruses of the leukosis-sarcoma complex tested which had subgroup B specificity were immunosuppressive while those of subgroup A were not. These results suggest that immunosuppression by these viruses may be related to subgroup specificity. (Author abstract) (49 Refs)

70. INHIBITORY EFFECT OF BOVINE SEMINAL RIBONUCLEASE ON ACTIVATED LYMPHOCYTE LYMPHOBLASTOID CELL LINES IN VITRO.

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Folia Biol (Praha); 27(5):334-345 1981

The effects of bovine seminal ribonuclease (AS RNase) and its four modified derivatives on pokeweed mitogen (PWM)-stimulated human lymphocytes, on mixed lymphocyte cultures, and on growth of four lymphoblastoid cell lines were examined. Native AS RNase, isolated as a dimer from bovine seminal vesical fluid, was used to prepare the carboxymethylated, succinylated, oxidized, and reduced forms of the enzyme. Native AS RNase exerted the strongest suppressive effect on phytohemagglutinin (PHA)-, PWM-, and mixed lymphocyte reaction-stimulated lymphocytes. At 5 and 100 ug/ml, AS RNase inhibited lymphocyte stimulation by 40 and 95%, respectively. The inhibitory effect persisted in the presence of a 20-fold increase in PHA. Simultaneous addition of AS RNase and (3H)thymidine to transformed lymphocytes did not affect thymidine uptake. AS RNase also had the strongest inhibitory effect on growth, viability, and DNA in the four lymphoblastoid lines tested. AS RNase decreased DNA synthesis in Molt-3 and UHKT-2 cells, with a decrease in live cell count compared to controls. Immunosuppressive effects of AS RNase suggest that the compound is one component of seminal plasma which may take part in suppression of immune responses of the female reproductive tract to spermatozoa. (21 Refs)

71. IN VITRO TRANSFER OF LEUKEMIC CELL IMMUNITY WITH XENOGENEIC IMMUNE RNA (MEETING ABSTRACT).

Weber B, Guerci O, Pierrez J, Marbache E, Belotti O, Janot C, Schooneman F
No affiliation given
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Lymphocyte transformation assays (LTA) were performed to demonstrate the transfer of leukemic cell immunity to healthy human lymphocytes in vitro with RNA extracted from lymphoid organs of sheep immunized with leukemic cells. RNA was extracted by the hot phenol method. RNA rich extracts were assessed for RNA DNA and protein concentration and analyzed by band sedimentation analytic ultracentrifugation on prep UV scanner. Soluble blast cell antigens were obtained by 3M KCl extraction. Normal lymphocytes previously incubated with RNA (90 g/10(5) cells) were cultured in presence of leukemic antigen. Tritiated thymide uptake was measured by liquid scintillation counting. Controls consisted of cultures of RNA treated or untreated lymphocytes with antigen, no antigen or phytohemagglutinin (PHA). Twelve sets of assays were achieved. Two types of results were observed. In 5 cases, the tritiated thymide uptake of RNA treated lymphocytes increased significantly when cultured with leukemic antigen at increasing protein concentration up to a threshold value and then decreased. No significant increase in tritiated thymide was observed when lymphocytes were not previously incubated with RNA. In all these cases RNA rich extracts contained RNA 12 S sedimentation fraction. In 7 cases RNA treated lymphocytes have no increase of tritiated thymide uptake with respect to ultracentrifugation no 12 S was found in 5 cases and was degraded in 2 cases. RNA was demonstrated not to have blocking or mitogenic properties in our experimental condition. Lymphocytes gave good reactivity as assessed by lymphocyte transformation assay in presence of PHA. The role of immune RNA in mediating tumor immunity is controversely regarded. We have pointed out lymphocytes need RNA 12 S to get sensitized. The effect of RNase treatment will be presented. (no Refs)

72. HUMAN MONOCYTES AND LYMPHOCYTES DIFFER IN THE RATE OF DNA REPAIR SYNTHESIS AND VIABILITY AFTER EXPOSURE TO NITROGEN MUSTARD.

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Acta Med Scand; 210(5):381-387 1981

Unscheduled DNA synthesis was studied in human lymphocytes and monocytes after treatment with nitrogen mustard, methyl-methane-sulfonate and ultraviolet irradiation. The unscheduled DNA synthesis was about 4x higher in monocytes than in lymphocytes after treatment with nitrogen mustard. Treatment with methyl-methane-sulfonate or ultraviolet irradiation confirmed the higher capacity for unscheduled DNA synthesis in the monocytes. When Ficoll-Isopaque-isolated mononuclear cells were exposed to various doses of nitrogen mustard and incubated for different periods, a dose- and time-dependent increase in trypan blue uptake was found. Furthermore, a corresponding dose- and time-dependent decrease was noted in 3H-uridine incorporation. Since trypan blue uptake will not enable differentiation between monocytes and lymphocytes appearing as a mixed cell population, 3H-uridine flash labeling index was studied after exposure to nitrogen mustard. There was a dose- and time-dependent decrease in 3H-uridine labeling index, suggesting a correlation between the absence of 3H-uridine incorporation and increase in trypan blue uptake. When compared to monocytes, the lymphocytes were more affected in this respect after exposure to nitrogen mustard. The possibility that differences in cytotoxic effect may be related to DNA repair mechanisms is discussed. (Author abstract) (34 Refs)

73. INHIBITION OF NK ACTIVITY BY SUGARS: EFFECT OF INTERLEUKIN 2.

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Ann Immunol (Paris); 132(3):327-337 1981

Effects of sugars, particularly D-mannose (DM), on the natural killer (NK) activity of fresh peripheral blood lymphocytes from normal donors and of cultured T lymphocytes (CTC) activated in a mixed lymphocyte reaction and incubated in a conditioning medium (CM), containing phytohemagglutinin (PHA), beta-interferon, and interleukin 2, were examined. DM produced a dose-dependent, linear decrease in NK activity with a mean inhibition of 60% with 100 mM DM. Other sugars, including xylose and sucrose, also inhibited NK activity; no specificity for D or L forms was observed. DM-induced inhibition of NK activity occurred via the effector cells: only preincubation of effector cells with DM during the 2 hr prior to testing inhibited NK activity. Increased cytotoxicity resulted when target cells (K562 human chronic myeloid leukemia cells) were preincubated with DM. NK activity was increased by 40% after incubation of cells in mixed lymphocytes culture and then CM. These CTC were resistant to DM-induced inhibition of NK activity. Preincubation of lymphocytes with beta-interferon increased NK activity by 120%; this NK activity was inhibited by DM. Preincubation of lymphocytes with PHA produced no NK activity resistant to DM inhibition. The results suggested that DM inhibition of NK activity is mediated by interleukin 2 and not by CM or interferon. (14 Refs) (In FRE)

74. TRANSFORMATION OF NORMAL HUMAN CORD LYMPHOCYTES BY CO-CULTIVATION WITH A LETHALLY IRRADIATED HUMAN T-CELL LINE CARRYING TYPE C VIRUS PARTICLES.

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Gan; 72(6):997-998 1981

Normal human cord WBC were co-cultured with lethally irradiated MT-2 cells to produce a T-cell line of cord WBC origin which harbored type C virus particles and adult T-cell leukemia-associated antigens (ATLA). On the 11th day of culture, 1 x 10(6) lethally x-irradiated (6,000 R) MT-2 cells were added to two of four dishes of cord WBC. Control cultures included two dishes of irradiated MT-2 cells without cord WBC and two dishes of cord WBC alone. All cultures were incubated at 37 C in a humidified 7.5% CO2 atmosphere. Two wk after co-culture, scattered foci of cell aggregates were observed on the sheets of macrophages. Continuous growth of cells developed in two of the co-cultured dishes, and this cell line, designated Ok, was maintained in culture for 3 mo. The Ok line consisted of mostly immature lymphoid cells with multinucleate giant cells. Sixty-six percent of the Ok cells formed spontaneous rosettes with neuraminidase-treated sheep RBC. Most of the Ok cells were positive for Leu-1 and OK11, but negative for Leu-2a and Leu-3a. None of the 145 Ok cells studied contained a Y chromosome; 41/46 cells had a 46,XX karyotype. Electron microscopy revealed many type C virus particles in the extracellular spaces. Most of the Ok cells were positive for ATLA when reacted with ATL patient's sera. The cultured cells gave a positive reaction with five sera from ATL patients but not with five sera from normal control individuals. These findings suggest that the type C virus was apparently transmitted from the MT-2 cells to the cord lymphocytes during co-cultivation. (8 Refs)

75. NK CELL SENSITIVITY OF THE LEUKEMIC K 562 CELLS; EFFECT OF SODIUM BUTYRATE AND HEMIN INDUCTION.

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J Immunol; 128(1):211-216 1982

Two differentiation inducers, hemin and sodium butyrate, have been studied for their effect on the NK sensitivity of human leukemic K 562 cells. When cultivated in the presence of 0.1 mM hemin, K 562 cells increased their hemoglobin synthesis. However, their susceptibility to NK lysis remained unaffected. On the other hand, sodium butyrate, which is known as a more potent differentiating agent, consistently reduced the NK sensitivity of K 562 cells and simultaneously induced the appearance of several differentiation markers. The effect of sodium butyrate on NK sensitivity was dose-dependent (maximal action at a 2-mM concentration), appeared after 2 days in culture, and was maximal after 5 days. After sodium butyrate removal from the culture medium, K 562 cells recovered their normal NK susceptibility within 4 days. In cold-target competition experiments, untreated K 562 cells acted as better competitors than butyrate-treated K 562 cells. Target-binding cell assays and specific NK cell removal on K 562 monolayers demonstrated that NK cells were less adherent to butyrate-treated than to control K 562 cells. From these data, it could be postulated that sodium butyrate modulates the expression of some target structure(s) involved in NK target binding. Five subclones of K 562 have been selected for exhibiting distinct, stable properties with regard to their cellular commitment (either to erythroid or to megakaryocytic lineage). The NK sensitivity of these subclones was roughly identical, and in all of them, butyrate treatment induced similar protection against NK-mediated lysis. Thus, the susceptibility to NK lysis and its modulation did not depend upon the predominant lineage present in each clone. (Author abstract) (32 Refs)

76. LYSIS OF FRESH HUMAN B-LYMPHOCYTE-DERIVED LEUKEMIA CELLS BY INTERFERON-ACTIVATED NATURAL KILLER (NK) CELLS.

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Int J Cancer; 29(1):1-7 1982

Fresh neoplasic B cells from 14 untreated patients with naturally occurring B-cell leukemias were found to be susceptible to lysis by human natural killer (NK) cells. The observed lysis of the fresh, non-cultured, neoplastic B cells was mediated by a population of interferon-augmentable, FcR-positive, non-adherent lymphoid cells, which were also able to kill the 'standard' NK target K562. A further finding was the correlation of NK susceptibility with disease available in 11 patients with chronic lymphocytic (CLL) and one patient with lymphosarcoma cell leukemia (LSCL). Enriched neoplastic B cells from seven untreated patients with non-progressive CLL, whose disease activity was stable throughout the 6 mo period of study, exhibited persistent and essentially unchanged NK susceptibility profiles. In contrast, four untreated patients with progressive CLL also had a measurable fraction of NK-susceptible, neoplastic targets, but these cells subsequently disappeared after successful cytoreductive therapy, and later re-emerged when these patients again developed progressive disease. Furthermore, one patient with LSCL was found to have persistent, measurable

NK susceptibility in his tumor-enriched fraction after unsuccessful cytoreductive therapy. An additional finding in the peripheral blood of patients with chronic B-cell leukemias was the presence of significantly lower NK effector-cell activity against K562 as compared to normal donor peripheral blood lymphocytes (PBLs). The implications of these findings are discussed. (Author abstract) (25 Refs)

77. ACTIVATION OF FC RECEPTOR-BEARING LYMPHOCYTES BY IMMUNE COMPLEXES. II. KILLER LYMPHOCYTES MEDIATE FC LIGAND-INDUCED LYMPHOKINE PRODUCTION.

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J Exp Med; 154(6):1868-1880 1981

The roles of the constant fragment (Fc) portion of IgG (Fc gamma) and of the Fc gamma receptors (FcR) in immune complex-induced lymphokine production (ICLP) were studied. Nonadherent lymphocytes enriched 3-to 4-fold in killer (K) cells and in other Fc gamma-binding cells showed antibody-dependent cellular cytotoxicity (ADCC) at approx 1/10 of the lymphocyte:target ratios required for unfractionated nonadherent lymphocytes. These K-cell enriched lymphocytes were induced by chicken antibody-sensitized RBC (EA), by aggregated human gamma globulin (AgHGG), or by sensitized P815 mouse mastocytoma cells to produce lymphocyte migration-inhibiting factor (LIF) at approx 1/10 of the concentration necessary for production of similar levels of activity by unfractionated cells. K cell but not natural killer (NK) cell depletion virtually eliminated ADCC and ICLP. K cells incubated with antibody-sensitized glutaraldehyde-treated P815 cells produced high levels of LIF in the supernatant; NK cells yielded little or no LIF activity when incubated with or without AgHGG. Isolated Fc gamma fragments stimulated nonadherent lymphocytes to produce high levels of LIF activity. Fc gamma fragments did not inhibit WBC migration but blocked EA-rosette formation by lymphocytes. Binding of Fc gamma ligands to FcR of the appropriate lymphocytes was the only requirement for ICLP. (49 Refs)

78. INCREASE AND INHIBITION OF PRE-B-CELL PROLIFERATION IN CULTURE, BY T CELLS.

Paolucci P, Layward L, Hayward AR, Rapson NT, Soothill JF
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Clin Exp Immunol; 43(2):336-341 1981

The effect of T cells on in vitro proliferation of pre-B cells (PBC) from marrow of patients with acute lymphatic leukemia (ALL) was studied. ALL-PBC occur in greater numbers in the marrow and proliferate in vitro more rapidly than PBC from normal individuals. PBC and B cells were obtained from 23 children (4-14 yr old, av age 8.5 yr) 1-6 mo after the end of successful treatment for ALL. The number of PBC was abnormally low in ALL patients during treatment but rose to abnormally high levels within 2 mo after withdrawal of treatment. Proliferation of PBC in vitro was decreased after removal of T cells by E-rosette formation. Proliferation was restored after addition of normal heterologous T cells. T cells from ALL patients (either syngeneic or heterogeneic) had a greater stimulatory effect on PBC proliferation than did normal T cells. T cells that had been exposed to 10 ug concanavalin A/ml suppressed PBC proliferation. Results indicate that T cells can either increase or reduce proliferation of PBC from bone marrow of children with ALL. This suggests that nonspecific effects of T cells are required for proliferation of PBC in vitro. The in vivo significance of T cell effects on PBC proliferation is uncertain. (12 Refs)

79. CONCOMITANT INDUCTION OF CYTOTOXIC AND SUPPRESSOR CELLS: MODULATION BY THEOPHYLLINE.

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Cell Immunol; 65(1):13-19 1981

Previous studies in man have shown that T cells with suppressor activity were mainly found among a subset bearing Fc receptors for IgG (T gamma). Recently, we found that virus-induced cytotoxic effector cells were also found predominantly among T gamma cells. In the present studies, we present evidence that similar, possibly overlapping T-cell populations can mediate both suppressor and cytotoxic activities when sensitized in vitro with virus-infected cells. In fact, both activities are found within the positively selected T gamma subset, but not in the T gamma-depleted population; both activities are abolished by irradiation but not by treatment with mitomycin C; a 1-hr exposition to theophylline at the onset of sensitization enhances both cytotoxic and suppressor activities. The data suggest that development of antiviral cell-mediated immune responses in vivo may also be accompanied by a concurrent induction of nonspecific suppressor cells. Such suppressor activity may play a role in the depressed cellular immune responsiveness which is associated with several systemic virus infections. (Author abstract) (25 Refs)

80. EFFECT OF HYPERTHERMIA ON HOST IMMUNOCOMPETENCE: EXPERIMENTAL STUDIES ON THE EFFECT OF IN VITRO HEATING ON MURINE AND HUMAN LYMPHOCYTE FUNCTION.

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Gan No Rinsho; 27(15):1820-1824,A-89 1981

Viability of mouse lymphocytes was reduced after in vitro heating (39 and 42 C, 1-5 hr) and was time and temperature-related. Hyperthermia (HP) depressed both cytotoxic activity of lymphocytes against MH-134 cells and phytohemagglutinin-induced blastogenesis. HP (42 C) also markedly decreased E-rosetting and blastogenesis of human lymphocytes. In some instances, human lymphocyte blastogenesis was enhanced after heating at 39 C. Results suggest hyperthermia may inhibit DNA synthesis in lymphocytes and cause damage to receptor sites. (14 Refs) (In JPN)

81. RESISTANCE OF NEONATAL HUMAN LYMPHOID CELLS TO INFECTION BY HERPES SIMPLEX VIRUS OVERCOME BY AGING CELLS IN CULTURE.

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J Infect Dis; 144(6):547-556 1981

Mononuclear leukocytes freshly harvested from human umbilical cord blood were refractory to infection by herpes simplex virus (HSV) Type 1, whereas cells aged in vitro for a wk produced 10-to 100-fold or greater more virus. Increased sensitivity of aged cells to infection by HSV was not dependent on active DNA synthesis by the cells at the time of exposure to HSV. The aging phenomenon was not due to the outgrowth of a specific cell subpopulation that is uniquely susceptible to HSV because increased sensitivity to HSV Type 1 occurred in a variety of cell subpopulations enriched or depleted of T lymphocytes, phagocytic cells, or adherent cells. About 25% of aged cells contained virions detectable by electron microscopy, considerably more cells than formed infectious centers. These virions were seen in large activated lymphocytes which are the principal cell subpopulation present in the aged cultures, but virions were also seen in small lymphocytes. (Author abstract) (21 Refs)

82. HUMAN T CELL SUBPOPULATIONS DEFINED BY A MONOCLONAL ANTIBODY. II. EVIDENCE FOR CELL COOPERATION IN THE RESPONSE TO ALLOANTIGENS AND GENERATION OF CYTOLYTIC CELLS.

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J Immunol; 128(1):20-23 1982

It has been shown previously that the 5/9 monoclonal antibody defines a small T cell subpopulation in human peripheral blood that includes all the cells responsible for proliferation to tetanus toxoid and to alloantigens as well as the helper cells for B cell differentiation. In the present study, human peripheral blood T cells were fractionated according to their reactivity with the 5/9 monoclonal antibody and stimulated in mixed lymphocyte culture (MLC). In spite of a strong proliferative response in MLC, 5/9+ cells generated no cytolytic activity against PHA-activated lymphocytes bearing the stimulating alloantigens (CTL activity) or against the K562 human cell line (NK activity). The precursors of these cytolytic effector cells were present in the 5/9-fraction. However, 5/9+ cells or soluble factors derived from 5/9+ cells were needed to induce 5/9-cells to respond in MLC and develop cytolytic activity. Both 5/9+ and 5/9-cell populations, upon MLC stimulation, were able to lyse L1210 mouse lymphoma cells in the presence of specific antibodies (ADCC). (Author abstract) (16 Refs)

83. NEUTROPHIL MIGRATION INHIBITION FACTOR FROM T LYMPHOCYTES (NIF-T): SELECTIVE REMOVAL OF BIOLOGIC ACTIVITY BY HUMAN PERIPHERAL BLOOD NEUTROPHILS, MYELOCYTIC LEUKEMIA CELLS, AND DIFFERENTIATED HL-60 CELLS.

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J Immunol; 128(1):457-462 1982

Neutrophil migration inhibition factor from T lymphocytes (NIF-T) is a newly recognized mediator that may regulate neutrophil function. In this report we show that normal and leukemic human peripheral blood neutrophils selectively removed NIF-T activity from conditioned medium. Removal of NIF-T activity was similar at 37 C and 4 C, neutrophil supernatants did not destroy NIF-T activity, and purified neutrophil plasma membranes removed NIF-T activity at zero degrees in contrast to the microsomal fraction of neutrophils, suggesting that membrane binding was responsible for neutrophil removal of NIF-T activity. The specificity of the removal of NIF-T activity by human neutrophils was indicated by the absence of detectable removal by human peripheral blood monocytes and alveolar macrophages and by neutrophils from other species. Moreover, cells from patients with acute and chronic myelocytic leukemia removed measurable NIF-T activity, whereas cells from a patient with acute myelomonocytic leukemia did not. In contrast to other human lymphoid and myeloid cell lines, only the human promyeloblast cell line, HL-60, removed NIF-T activity. Uninduced HL-60 cells removed only about 7% of the NIF-T activity removed by neutrophils. Differentiation of HL-60 cells by exposure to dimethyl sulfoxide, however, enhanced the removal capacity for NIF-T to that of peripheral blood neutrophils, and differentiated HL-60 cells responded to NIF-T in the migration assay. The responsiveness of differentiated HL-60 cells to NIF-T was, however, markedly impaired. Monocytes differentiated from HL-60 by 12-O-tetradecanoylphorbol-13-acetate did not remove measurable NIF-T activity. These results suggest human neutrophils and neutrophil precursors express specific binding sites for NIF-T. (Author abstract) (37 Refs)

84. INFLUENCE OF IN VITRO IRRADIATION UPON LIF PRODUCTION BY CONA STIMULATED MONONUCLEAR CELLS.

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Int J Radiat Oncol Biol Phys; 7(12):1679-1683 1981

The effect of in vitro irradiation on production of leukocyte migration inhibitory factor (LIF) by lymphocytes stimulated with Concanavalin A (ConA) was studied. Human mononuclear cells (MNC) from healthy individuals were cultured with or without 90 min pulse exposure to 80 ug ConA/ml. MNC cultures were exposed to irradiation (150 to 1,200 rads within 30 min) before or after exposure to ConA. Irradiation before or after ConA stimulation did not impair LIF production compared to that of non-irradiated MNC. Irradiation produced moderate but significant increases in LIF production in some cultures, mainly those from donors showing poor LIF release after ConA stimulation. MNC culture supernatants that were pretreated with rabbit anti-LIF antibodies had no inhibitory effect on migration of human granulocytes or guinea pig peritoneal exudate cells, indicating the specificity of LIF. Radioresistance of LIF stimulation suggests that LIF production does not require cell proliferation. The increase of LIF production in irradiated MNC cultures suggests that a suppressor-cell population exists that is radiosensitive. Results of the study have implications for immune changes in patients undergoing radiotherapy. (28 Refs)

85. EFFECTS OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE AND MEZEREIN ON GAMMA RADIATION-INDUCED DNA REPAIR IN RESTING BOVINE LYMPHOCYTES.

Perrella FW, O'Leary P, Boutwell RK
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Cancer Lett; 15(1):87-93 1982

The effect of the potent tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) on gamma radiation-induced DNA repair in resting (Go) lymphocytes was studied. Lymphocytes were irradiated with appropriate doses of gamma radiation in order to introduce single-strand breaks in their DNA. The repair of DNA damage was determined by incubating irradiated (500 rad) cultures at 37 C in a water bath and at various times placing them on ice. Mezerein, a non-promoter but a co-mitogen in lymphocytes was used as a control agent. The cells were lysed immediately following irradiation on linear sucrose gradients and the distance travelled by the nucleotides was determined. The sedimentation ratio was calculated from the distance travelled by nucleoids for irradiated cells to that of unirradiated cells. It was observed that the presence of 1 uM of either TPA or mezerein in lymphocyte cultures following a 1 hr incuba tion did not produce a significant deviation in sedimentation behavior from dimethyl sulfoxide treated control cultures. Results indicate that neither TPA nor mezerein at 1 uM h have any degenerative effect on the integrity of the cells DNA. The percent recovery of DNA supercoil in nucleoids following 1 hr incubation of irradiated cells was 30-34% whether or not TPA or mezerein was present during recovery period. Results support the hypothesis that the tumor promoting ability of TPA is not a result of impaired repair of potentially mutagenic lesions in DNA. (20 Refs)

86. THE ROLE OF T CELL SUBSETS AND IA ANTIGENS IN DELAYED-TYPE HYPERSENSITIVITY.

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Int Arch Allergy Appl Immunol; 66(Suppl1):197-203 1981

Analyses of delayed-type hypersensitivity (DTH) in the mouse are presented: factors involved in its regulation with particular reference to low mol wt WBC extract and transfer factor; relationship with antibody responses; and disturbances in T cell interactions leading to impaired immune competence with age. In connection with changes associated with aging, it is noted that an interesting parallel can be drawn between the high incidence of neoplasia associated with chronic graft versus host responses and that found in human renal transplant recipients. In both conditions, chronic antigenic stimulation across a major histocompatibililty gene complex barrier is accompanied by primary or secondary suppression of the immune system. Conditions can then be regarded as favorable for subversion of immune surveillance either by the immunostimulation of Prehn or by sneaking through, a phenomenon which may be mediated by suppressor T cells. Furthermore, it is noted that most tumors which arise consist of lymphomas and epithelial tumors, both of which can be derived from Ia+ cells and are well recognized forms of malignancy in old age. (33 Refs)

87. IMMUNOREGULATION BY BLASTS FROM NULL CELL AND T-CELL LEUKEMIAS: HELP AND SUPPRESSION OF T-CELL PROLIFERATIVE RESPONSES TO MITOGENS.

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Cancer; 49(1):43-47 1982

The immunoregulatory activity of bone marrow leukemic blasts from five patients with null-cell acute lymphoblastic leukemia (ALL) and two children with T-cell ALL was evaluated. Blasts were studied in co-culture for their effects on the proliferative responses of normal allogeneic peripheral blood lymphocytes to phytohemagglutinin. Mitomycin C-treated null cell ALL blasts from two of five children suppressed the proliferative responses of normal responder cells by 80% and 58% whereas those from two other children enhanced the responses by 118% and 31%. T-cell leukemic blasts from one patient with T-cell ALL exhibited helper cell activity (26%) and T-leukemic blasts from the other demonstrated suppressor cell activity (53%). The helper cell activity of leukemic blasts was associated with stimulating capacity of null blasts in one-way mixed lymphocyte reactions. In six of seven cases, incubation of blast cells with concanavalin A (20 ug/ml) for 48 hr prior to co-culture with responder cells did not result in the generation of significant suppressor cell activity. Our study suggests that leukemic blasts from certain patients with 'null' and T-cell ALL may possess spontaneous helper or suppressor cell immunoregulatory activity. The functional heterogeneity of leukemic blasts may help in subclassifying the ALL. (Author abstract) (22 Refs)

88. THREE NEW AGENTS FOR IMMUNOTHERAPY TRIALS: AZIMEXON, BESTATIN, AND TUFTSIN.

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Recent Results Cancer Res; 80:331-333 1982

Three new immunotherapeutic agents are reviewed. Azimexon and tuftsin have stimulated all T cell functions, B cell antibody production, natural killer cell activity, and macrophage cytotoxicity in tests with mice. Bestatin has potentiated T-dependent and T-independent humoral responses and has activated macrophages. Clinical tests have shown that azimexon and bestatin increase delayed-type hypersensitivity in anergic patients. (20 Refs)

89. LONG TERM CULTURE OF HUMAN T-CELLS IN THE PRESENCE OF T CELL GROWTH FACTOR (TCGF) FROM HUMAN TONSILS (MEETING ABSTRACT).

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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

In the presence of supernatants of human WBC cultures, mitogen activated T-cells are growing in continued culture. The proliferative response of the cultured T-cells (CTC) is dependent on the source of the TCGF used. In contrast to human peripheral blood WBC (PBL) human spleen cells represent an excellent source of TCGF. Due to the more convenient availability, we were interested to look at the proliferative activity of supernatants from human tonsils. We sensitized mononuclears from human tonsils (5 x 10(6)/ml) with phytohemagglutinin (PHA). Supernatants were assayed for their proliferative activity of CTC by stimulation for 3 days during the 4th passage of a 12 day old T cell culture, followed by a 12 hr 3H deoxythymidine (TdR) pulse. Human tonsil cells produced high levels of TCGF with dose response curves similar to those observed with spleen cells. Some donors were low producers. Growth kinetics showed a five -fold increase of seeded cells every 72 hr. We conclude that mononuclears from human tonsils are able to produce TCGF upon stimulation with PHA. In contrast to spleen cells, there was a considerable difference in TCGF production between individual tonsil donors. Supernatants from human tonsils induced selective continuous proliferative growth of T-lymphocytes from mononuclears of healthy individuals as well as from leukemic patients during remission. (no Refs)

90. PHASE I TRIAL WITH THE IMMUNOTHERAPEUTIC AGENT OK-432 (MEETING ABSTRACT).

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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

The streptococcal preparation OK-432 has been intensively investigated for its immunomodulating and therapeutic efficacy in cancer patients mainly in Japan. In a Phase I trial, including 35 patients with malignant melanoma for possible side effects of this preparation when given im, iv, id, it, intrapleural or ip. Iv route and intracavitary application always led to rise of body temperature, being the only one side effect observed. Clinical outcome was evaluable in 22 patients with advanced malignant melanoma having received several doses of OK-432 by a variety of routes for a longer period of time. It may be considered favorable in 14 of them, including one complete remission of pulmonary metastases maintained for more than 4 mo by continuous therapy. Immunopharmacological studies showed that iv and id injection of one single dose (1 KE) of OK-432 is significantly enhancing natural killer cell activity with a max on day 3 when measured in a 4-hr chromium-51 release assay against K562 targets. Intrapleural application, furthermore, led to a reduction of suppressor cells against natural killer cells, which we have demonstrated to be present in malignant pleural effusions. Furthermore, we were able to demonstrate that in vitro incubation patients's lymphocytes with OK-432 significantly enhanced lymphocyte cytotoxicity in a dose-dependent manner comparable to that of Hu IFN. According to our studies, OK-432 seems to be a potent immunomodulator which also shows some clinical efficacy even when given to patients with advanced malignant disease. (1 Ref)

91. IN VITRO AND IN VIVO INDUCTION OF CYTOTOXIC LYMPHOCYTES BY INTERLEUKIN 2 (IL2) (MEETING ABSTRACT).

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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

IL2 is a lymphokine released from helper t cells which is necessary for the gene ration of cytotoxic L lymphocytes. The purpose of this study was to examine whether stimulation of lymphocytes in vitro and in vivo with IL2 would induce cytotoxic T cells against autologous melanoma cells. IL2 was isolated from 24 hr phytohemagglutinin (PHA) stimulated lymphocyte supernatants by membrane chromatography. Incubation of lymphocytes from melanoma patients in IL2 (2u/ml) for 6 days resulted in generation of cytotoxic cells against autologous and allogeneic melanoma and non-melanoma target cells. Cold target inhibition studies suggested the latter was due to killing by natural killer or activated T cells. Killing of autologous melanoma cells appeared to be due to T cells specific for these cells. In vivo injection of IL2 containing supernatants in 2 patients (no PHA) resulted in a number of changes in the immune system but at 5 to 7 days cytotoxic lymphocytes against allogeneic and autologous melanoma cells were detected which lasted for several days. Data on IL2 clearance rates and other immunological data will be presented. These results suggest that IL2 may be a relatively non-toxic but effective agent for the induction of cytotoxic T cells against melanoma and may have an important role in immunotherapy. (no Refs)

92. GENERATION IN VITRO OF HLA-RESTRICTED EB VIRUS-SPECIFIC CYTOTOXIC HUMAN T CELLS BY AUTOLOGOUS LYMPHOBLASTOID CELL LINES: THE ROLES OF PREVIOUS EB VIRUS INFECTION AND FOETAL CALF SERUM.

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Int J Cancer; 29(1):41-48 1982

The cytotoxic response of human lymphocytes to the autologous lymphoblastoid cell line (LCL) was investigated with five Epstein-Barr virus (EBV)-seropositive and four seronegative donors and an additional donor who seroconverted during the course of the study. Without exception, the cytotoxic T cells generated in 7-and 14-day LCL-stimulated cultures from seropositive donors were strongly lytic for the autologous LCL. Overall, the cytotoxic T cells generated in cultures from seropositive donors showed a striking preferential lysis of the autologous LCL and cross-reactive killing of allogeneic LCL target cells matched for certain HLA-B antigens. Lysis of the K562 line was consistently negligible. In comparison to the considerable self-preferred lysis obtained with T cells from LCL-stimulated cultures, the level of autologous killing by T cells generated in control unstimulated cultures was relatively low. The cytotoxic patterns obtained with cytotoxic T cells generated in cultures from seronegative donors were markedly different from those obtained with seropositive donors. The level of autologous killing by T cells harvested from LCL-stimulated cultures was considerably lower than that obtained with seropositive donors and often did not increase above that seen in control cultures, except at the highest stimulatory dose. Moreover, preferential lysis of the autologous LCL target cells by T cells from LCL-stimulated cultures was essentially due to the fetal calf serum (FCS)-induced cytotoxicity, and there was no obvious HLA-antigen-restricted killing of allogeneic target cells. Lysis of K562 target cells was generally more pronounced at the highest level of stimulation than that observed with seropositive donors. The distinctive cytotoxic T-cell response patterns observed with the seropositive and seronegative donor cultures were both observed with cultures from an individual donor who was tested before and after infectious mononucleosis. With LCL-stimulated cultures from seropositive donors, the cytotoxic T-cell response to autologous LCL is predominantly directed against EBV-associated antigens and is HLA-antigen restricted. In contrast, with seronegative donor cultures, the cytotoxic T-cell response is primarily due to FCS-induced cytotoxicity, although a response against other LCL-associated antigens may be superimposed in cultures stimulated with high levels of autologous LCL. (44 Refs)

93. ANTI-TUMOR EFFECT OF SYNGENEIC SPLEEN CELLS TREATED WITH IMMUNE RNA AND TUMOR ANTIGEN.

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Int J Cancer; 29(1):113-117 1982

The antitumor effect of syngeneic spleen cells, xenogeneic immune RNA (I-RNA) and tumor antigen (TA) was studied in a chemically induced (N-methyl-N-nitrosourethane) colon carcinoma model in BALB/c mice. When the mice were treated, sequentially, with these three elements by local injection under the tumor, complete tumor regression was observed in 25% of the animals. Complete tumor regression was observed in 17% of animals treated by injection of spleen cells pre-incubated with I-RNA in vitro followed by an injection of TA. When spleen cells were treated first with I-RNA and then with mitomycin-C, therapeutic benefit was obtained and the survival rate of mice treated with these spleen cells and TA was significantly higher than that of the control group (no treatment). The antitumor effect of this treatment was abrogated completely when spleen cells were treated with mitomycin-C prior to I-RNA incubation. When spleen cells were incubated with TA in vitro or after incubation with I-RNA and then injected into tumor-bearing mice, no antitumor effect was noted. These data suggest that DNA synthesis and/or lymphocyte proliferation is essential for the action of I-RNA in sensitizing lymphocytes but not essential in the interaction of I-RNA-sensitized lymphocytes with TA. In addition it appeared that, under the conditions used, the participation of host factors was essential in the latter interaction, since treatment of I-RNA-sensitized lymphocytes with TA in vitro was ineffective. (Author abstract) (13 Refs)

94. LYSIS OF TUMOR BIOPSY CELLS BY AUTOLOGOUS T LYMPHOCYTES ACTIVATED IN MIXED CULTURES AND PROPAGATED WITH T CELL GROWTH FACTOR.

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Dept. Tumor Biology, Karolinska Inst., S-104 01, Stockholm 60, Sweden
J Exp Med; 155(1):83-95 1982

Lymphocytes of patients activated in mixed lymphocyte culture (MLC) lysed allogeneic third-party cells and in some cases also lysed autologous tumor cells. Allogeneic but not autologous phytohemagglutinin (PHA) blasts were also damaged by these effectors. The cytotoxic potential of MLC-activated lymphocytes from healthy donors was similar: allogeneic tumor and PHA blasts but not autologous PHA blasts were lysed. The cytotoxicity of lymphocytes activated in autologous tumor cells were specific for the stimulator because they acted only on the autologous tumor cells. Results obtained in cold target competition assays suggested that activated lymphocytes lyse the third party tumor targets because of alloantigen recognition and in MLC, several different sets of alloreactive cytotoxic lymphocytes are present simultaneously. There all-reactive cells are different to those that act on autologous tumor cells. The lysis of allogeneic tumor cells by lymphocytes of the patient is probably not due to recognition of cross-reacting tumor related antigens, and the antitumor cytotoxicity of the patients' MLC-activated lymphocytes is due to specifically reacting cells. (40 Refs)

95. EFFECTS OF CYCLOPHOSPHAMIDE ON T SUBSET FUNCTION.

Ozer H, Cowens JW, Colvin M, Nussbaum-Blumerson A, Sheedy D
Dept. Medical Oncology and Clinical Pharmacology, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Exp Med; 155(1):276-290 1982

The in vitro sensitivity of functional human T cell subsets to 4-hydroperoxycyclophosphamide (4-HC) was examined in a poly clonal B cell differentiation assay and in the generation of mitogen-induced suppressor cells for effector B cell function. These results demonstrated that human presuppressor cells for B-effector function are very sensitive to low concentrations of 4-HC whereas native cells with suppressor and induce functions are resistant when tested in vitro. The effects of 4-HC on suppressor T cells appear to occur at concentrations which as not result in DNA cross-linking or decreased blastogenesis. (26 Refs)

96. THE ROLE OF IA IN T-CELL ACTIVATION.

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Transplant Proc; 13(4):1843-1845 1981

The role of IA region antigen in T-cell activation is discussed. Antigen-specific proliferation of primed T cells requires the presentation of antigen on histocompatible, IA-positive, adherent cells (APC). Recent advances in the field of interleukins suggest an alternate model in which the T cell recognizes antigen on the macrophage and activates the macrophage to produce IL1. T cells become activated after interaction with antigen and IL1 and develop receptors for IL2. Other T cells become activated and produce IL2, which has T-cell growth factor activity. The production of 'helper factor' is blocked by anti-Ia sera in a number of experimental models. Helper factor is a mixture of IL1, IL2, and a third factor, TRF. The production of IL1 is blocked by the presence of monoclonal anti-Ia; as a consequence of the block, no IL2 or TRF is produced. The production of IL2 can be restored by addition of IL1. The antigen stimulation of the IL2 producer cell does not require an IA-positive cell. Cultures of a long-term alloreactive T-cell line (C.C3.11.75) produce TRF factor. The line is specific for a private specificity of IAk and responds when stimulated with the antigen. The production of TRF in response to self + X must involve IA-restricted interaction with a macrophage or a B cell. Whether other T-cell interactions with antigen are IA restricted is not yet known. (7 Refs)

97. FACTORS INFLUENCING THE VACCINIA-SPECIFIC CYTOTOXIC RESPONSE OF THYMOCYTES FROM NORMAL AND CHIMERIC MICE.

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Transplant Proc; 13(4):1850-1853 1981

Following adoptive transfer into irradiated recipients, thymocytes can be induced to respond strongly to vaccinia virus. High levels of cytotoxic T-lymphocyte (CTL) activity may be generated from thymus, but not from spleen, of 3-day-old mice. The capacity of thymocytes to differentiate into effector CTL tends to be lost with age. Some of this loss may reflect positive suppression: a single, low dose of cyclophosphamide allows the reemergence of responsiveness in at least one mouse strain. Thymocytes from [A (A x B)F1] and [(A x B)F1 A] chimeras show the response patterns that would be predicted from previous studies of lymph node and spleen cells. However, thymic function seems to be rapidly lost in the [A (A x B)F1] chimeras. (Author abstract) (7 Refs)

98. THE IMMUNOGENIC AND TUMORIGENIC PROPERTIES OF A MURINE LYMPHOMA THAT EXPRESSES FOREIGN ALLOANTIGENS: ROLE OF HELPER FACTOR(S) IN GENERATING A CYTOTOXIC RESPONSE IN VITRO.

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Transplant Proc; 13(4):1867-1873 1981

Mice of haplotypes that did (SJL, BALB/c, and C57BL/6) and did not (C3H/He) share antigens expressed on CH-1 cell line were selected, and the in vitro cytotoxic responses of the various haplotypes against CH-1 and the growth of CH-1 in vivo were examined. CH-1 was not tumorigenic in SJL, C57BL/6, or C3H/He mice. These strains generated a strong cytotoxic response against CH-1. CH-1 was lethal when injected into BALB/c mice. BALB/c responder cells generated only a weak in vitro cytotoxic response against CH-1. Potentiation of the BALB/c anti-CH-1 cytotoxic response by helper factors was investigated. The addition of helper supernates resulted in a threefold increase in percent specific lysis when compared with effectors generated in the absence of added helper factor. This increase in cytotoxic activity was observed at all three effector-to-target cell ratios tested. Deletion of nylon wool adherent cells from the responding population eliminated the development of a detectable cytotoxic response. Cytotoxic T lymphocytes specific for CH-1 were generated from nylon wool nonadherent cells when helper factor was provided during the sensitization phase. The generation of cytotoxic effector cells was dependent on helper factor and antigen stimulation. Helper factors induced by either bacterial antigens or cell-bound alloantigens assisted the development of specific effector cells. (16 Refs)

99. H-2 RESTRICTION OF THE CELLULAR RESPONSE IN A METHYLCHOLANTHRENE SARCOMA SYSTEM STUDIED WITH AN F1 TUMOR AND ITS H-2 LOSS VARIANTS.

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Transplant Proc; 13(4):1874-1876 1981

Restriction of a T-cell response against the tumor-specific transplantation antigen (TSTA) by H-2 was studied by providing a suitable system using reciprocal H-2 loss variant sublines derived from an F1 tumor. Two sublines of an (AxA.SW)F1 methylcholanthrene-induced sarcoma (MSWB), were used. The MSWB-A subline selected for growth in A/Sn has lost H-2s and the MSWB-S subline grows in A.SW and lacks H-2a alloantigens. The H-2 make-up of the tumors was determined by serology and reactivity with alloreactive cytotoxic T lymphocytes. Immunization of (AxA.SW)F1 mice with M-AS, M-A, or M-S generated transplantation immunity against any of these tumor cells. The cross-protection proved that the F1 tumor and its H-2 loss variants shared the same TSTA. The effect of (AxA.SW)F1 cells was not influenced if the culture contained sensitizers. The A.SW cells were stimulated for higher cytotoxic activity. (AxA.SW)F1 cells killed both M-A and M-S cells, but the effect against M-S was considerably weaker. Results suggest the involvement of antiparental response because the lymphoid cells from F1 mice immunized with each other of the three tumors killed not only the A tumor but also A/Sn blasts. A/Sn effectors obtained from mice immunized with any of the three tumors killed all three targets, through the effect against A tumor was the strongest. The anti-M-S was strengthened if the cultures contained either M-AS or M-S but not M-A. There was no indication for dose dependency. The mechanisms could be that two types of antitumor killer cells are generated in the A.SW. One subset recognizes the TSTA in association with the H-2s alloantigen and the other is not H-2 restricted. (3 Refs)

100. CHARACTERIZATION OF ALLOANTIGEN-ACTIVATED HUMAN LYMPHOCYTES CYTOTOXIC FOR AUTOLOGOUS EB VIRUS-TRANSFORMED LYMPHOBLASTOID CELL LINES.

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Transplant Proc; 13(4):1893-1896 1981

Previously reported results on the ability of cytotoxic T lymphocytes (Tc) or natural killer (NK)-like cells to mediate lysis of autologous Epstein-Barr virus-transformed lymphoblastoid cell lines (LCL) by lymphocytes stimulated with pooled allogeneic normal cells are summarized. Studies of the effect of 5-bromodeoxyuridine and light on generation of cytotoxic cells capable of lysing autologous LCL cells indicated that alloantigen-induced effector cells that lyse autologous LCL cells are similar to those lysing allogeneic normal cells. Treatment of fresh lymphocytes with monoclonal antibody OKT3 (reactive with greater than 95% of RBC-rosetting cells) or OKT8 (reactive with a subpopulation of T cells) and complement (C') did not reduce NK activity against K562 leukemia cells. Treatment of fresh lymphocytes with monoclonal antibody OKM1 (reactive with macrophages and a small proportion of nonadherent cells) and C' decreased NK cell activity by approx 75%. Thus the majority of NK cells appear to be OKT3-, OKT8-, OKM1+. The phenotype of mixed WBC culture (MLC)-generated cells that lyse autologous LCL was the same as that of Tc which lyse allogeneic normal cells (OKT3+, OKT8+); NK-like cells generated in MLC, which lyse K562 cells, were OKT3-, OKT8-. The results indicate that lysis of autologous LCL cells by pool-stimulated cells is mediated by Tc. (16 Refs)

101. ACTIVATION OF ALLOSENSITIZED MEMORY LYMPHOCYTES INTO SECONDARY CYTOTOXIC T LYMPHOCYTES BY THIRD-PARTY STIMULATOR CELLS: GENETIC MAPPING OF THE STIMULATING ANTIGENS.

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Transplant Proc; 13(4):1897-1900 1981

Cytotoxicity of secondary cytotoxic T lymphocytes (CTL) activated in in vitro mixed WBC cultures (MLC) by third-party stimulators was studied. BALB/c (H-2d) secondary CTL with specificity for C57BL/6 (H-2b) target alloantigens were activated by third-party H-2 disparate, SJL/J (H-2s) and C3H (H-2k) lymphocytes. Stimulator cells syngeneic to responder cells did not activate secondary CTL. Unlike memory lymphocytes, normal lymphocytes only expressed cytotoxic activity against H-2b target cells when stimulated with H-2b, and not when cultured with H-2k or H-2s stimulator cells. Secondary CTL activated by specific or third-party stimulator cells displayed cytotoxic activity against third-party targets and lower, but comparable cytotoxicity against specific targets. Disparities in non-H-2 alloantigens present on H-2 compatible B10.D2 and DBA/2 stimulator cells were not sufficient to activate allosensitized BALB/c (H-2d) memory lymphocytes. The ability of splenocytes from congenic, H-2 incompatible inbred strains of mice, B10.BR (H-2k) and B10.S (H-2s), to stimulate a secondary cytotoxic response suggested that the activating antigens were encoded by genes in the H-2 complex. The genes were located in the G-D regions of the H-2 complex. (14 Refs)

102. COLLABORATION OF POLYMORPHONUCLEAR LEUKOCYTES (PMN) WITH CON-A-STIMULATED LYMPHOCYTES IN THE INHIBITION OF TUMOR GROWTH.

Sendo F, Seiji K, Watabe S, Fuyama S, Arai S, Nathanson SD, Truitt RL, Thomson DM, Lenox ES

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Transplant Proc; 13(4):1927-1928 1981

Stimulation of polymorphonuclear WBC (PMN) by supernatant of concanavalin-A (Con-A)-stimulated lymphocytes was studied. When inhibition of 3H-thymidine uptake of KMT-17 cells was tested with 48-hr culture supernatant of Con-A-stimulated lymphocytes, culture supernatant showed cytostatic activity against KMT-17 cells. Addition of PMN to supernatant increased the inhibition of tumor cell growth; PMN itself showed no cytostatic activity. When various numbered PMN were added to 72-hr supernatant, inhibition of 3H-thymidine uptake was observed, although PMN alone showed no cytostatic activity. Inhibition of tumor growth showed dose response to number of PMN and to concentration of supernatant. The results suggest that Con-A-stimulated lymphocytes release certain lymphokines that activate PMN (PMN-activating factors) in the inhibition of tumor growth. The PMN-activating factors were relatively stable under physicochemical treatment. (2 Refs)

103. EXPERIMENTAL MODELS FOR GRAFT-VERSUS-HOST REACTION IN MICE.

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Fukuoka Igaku Zasshi; 72(9):502-520 1981

Graft-versus-host (GVH) reactions were studied in crosses of mouse strains that differed with respect to histocompatibility antigens. Crosses (ABF1) of AKR and C57BL/6 mice (strains having differences in H-2 histocompatibility antigen), crosses (ACF1) of AKR and C3H/He mice (strains having differences in non-H-2 histocompatibility and M locus antigens), and progeny of male and female C57BL/6 mice (the different sexes having differences in H-Y antigens) were used to analyze the following GVH reaction parameters: occurrence of splenomegaly, runt disease, and cytotoxic T-lymphocytes (CTLs). Methylcholanthrene-induced tumor cells were used as target cells. Under certain circumstances, both ABF1 and ACF1 mice had s trong GVH reactions, despite minor differences in antigens. Also, despite pretreating immunity-bearing cells with syngeneic antigens and complete Freund's adjuvant, it was difficult to prevent the appearance of CTLs and runt disease in crosses such as the ACF1. The H-Y antigen was found to be an important factor in selecting donors and recipients of bone marrow transplants. The findings suggested that a GVH reaction can occur even with minor differences in antigens between donors and recipients; thus, adequate investigation of serum factors and of mixed lymphocyte cultures should be carried out prior to bone marrow transplantation. (68 Refs) (In JPN)

104. IMMUNOPOTENTIATING ACTION OF STREPTOCOCCAL PREPARATION OK-432 AND PROTEIN-BOUND POLYSACCHARIDE PS-K ON DEPRESSED STATE OF CELL-MEDIATED AND HUMORAL IMMUNITIES OF FRIEND LEUKEMIA VIRUS INFECTED MICE.

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Dept. Internal Medicine, Sch. Medicine, Kitasato Univ., Japan

Nippon Gan Chiryo Gakkai Shi; 16(4):641-646 1981

The effects of OK-432, a penicillin-treated Group A hemolytic streptococci, and PS-K, a protein-bound polysaccharide, on the immune response of male ICR and ddY mice infected with Friend leukemia virus (FLV) were examined. FLV-infected mice were injected iv with either 0.5 KE (1 KE = 0.1 mg lyophilized streptococci) OK-432 or 30 mg/kg PS-K daily for 3 consecutive days, from 5 days before and from 3 days after FLV inoculation. Lymph node cells of mice treated with both FLV and OK-432 responded well to ovalbumin (OA) and purified protein tuberculin derivative in macrophage migration inhibition tests conducted 21-31 days after immunization with OA. Mice treated wtih FLV and PS-K showed no response. Both response of hemolytic plaque forming cells to sheep RBC (anti-SRBC PFC) and serum antibody production were not detected in the FLV-infected mice, whether injected with OK-432 or PS-K. The anti-SRBC PFC response and antibody production in OK-432-treated mice were slightly greater than those in the other FLV-infected groups, but the differences were not significant. The results suggested that OK-432 has an immunopotentiating activity on the depressed state of cell-mediated immunity, while PS-K does not. Neither PS-K nor OK-432 enhanced humoral immunity in FLV-infected mice. (13 Refs)

105. THE IMMUNOREGULATORY CHARACTERISTICS OF THE LACTIC DEHYDROGENASE VIRUS (LDV), A COMMON CONTAMINANT OF TUMORS.

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Cell Mol Biol; 27(2/3):83-96 1981

A tumor-enhancing and antibody increasing spleen cell-associated factor originating in Lewis lung carcinoma (3LL)-bearing C57BL/6 mice was identified as the lactic dehydrogenase virus (LDV). A potent immunoregulating factor was obtained only following the inoculation of LDV-infected but not LDV-f ree tumor cells. The observed augmentation of humoral responses by an acute infection with LDV was found to be fully correlated with the ability of the virus to replicate and establish a persisting infection in the host. LDV caused an augmented humoral response in all mouse strains tested (causing a life-long viremia), but failed to influence the humoral response in rats, which are an LDV-resistant species. We found that although an infection with LDV causes a polyclonal B-cell activation it does not affect all of the different B-cell clones and in the presence of a specific antigenic stimulus it preferentially triggers the IgG2 subclass of antibody-secreting B cells. An acute LDV infection causes a substantial suppression of cell-mediated immunity functions and a delayed thyroid allograft rejection was demonstrated in infected mice. Since mononuclear phagocytes, which are the target cells of LDV, play an important role in cellular immune responses, we tested the immunogenic antigen-presenting capacity of LDV-infected macrophages, using a system in which in vitro reactivation of memory T cells is dependent upon effective specific antigen presentation by macrophages. We found that the antigen presentation capacity of macrophages from acute LDV-infected mice is impaired. These results may contribute to a better understanding of the ways in which mammalian RNA viruses may act as immunomodulators. (Author abstract) (42 Refs)

106. TOXICITY, IMMUNOSUPPRESSIVE, AND CYTOTOXIC EFFECTS OF SOME ANTINEOPLASTIC AGENTS.

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Dept. Pharmacology, N. I. Pirogov Second Medical Inst., Moscow, USSR
Farmakol Toksikol; 44(6):718-721 1981

Immunosuppressive and cytotoxic effects of the antineoplastic agents pafencil (PF), C-119, C-72, bleomycin (BL), and L-aspariginase (LAS) were studied in CBA mice. The PF, C-72, and BL were more toxic than the C-119 and LAS. The alkylating agents (PF, C-119, and C-72) provided more pronounced inhibition of antibody-producing cells and rosette-forming cells than did the BL and the LAS. The most pronounced inhibition of number of nucleated splenocytes was observed after the administration of the LAS. (17 Refs) (In RUS)

107. STUDIES ON INTERACTIONS BETWEEN PLASMINOGEN ACTIVATOR-CONTAINING FLUIDS AND AVIAN AND MURINE LYMPHOCYTES.

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Dev Comp Immunol; 5(4):649-660 1981

The ability of plasminogen activator (PA) from culture fluids of avian virus (AVS)-transformed chicken embryo fibroblasts (CEF) and avian sarcoma cells to serve as a lymphocyte mitogen and to modulate lymphocyte response was studied. High levels of PA and fibrinolytic activity were associated with both types of tumor cells induced by ASV. Tumor levels were 1.5-8x greater than than those of ASV-transformed CEF. Of 10 culture fluids, 2 from normal and 8 from ASV-transformed CEF cells, 9 possessed non-specific mitogenic capacity. No mitogenesis was associated with 2/2 cultures from normal CEF cells and with 3/8 cultures from ASV-transformed CEF cells. These latter preparations contained little or no demonstrable PA activity. Both papain and trypsin were stimulatory to avian lymphocytes within a narrow range of concentrations. Nonspecific mitogenesis of Balb/c mouse splenic lymphocytes could only be effected by those culture fluids which contained significant levels of PA activity. Urokinase was also mitogenic for mouse lymphocytes. The inhibition of mitogenesis by PA antagonists was examined. Results of studies of the immunomodulating effects of culture fluids and urokinase suggested that the mitogenic effect of PA may be dependent on cofactors. Circumstantial evidence that PA may act as a lymphocyte mitogen was provided. (17 Refs)

108. ANTIGENIC AND GENETIC PARAMETERS IN THE STIMULATION AND IN THE LYTIC PHASES OF ANTI-HAPTEN + SELF CYTOTOXIC T CELLS AND THEIR DERIVED CLONES: ROLE OF THE T HELPER CELL.

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J Supramol Struct Cell Biochem; 16(4):359-370 1981

Requirements for stimulation of cytotoxic T cells (CTL) and for their lytic recognition were compared in T cell lines repeatedly stimulated with trinitrobenzene sulfonate-treated syngeneic murine spleen cells. Differences were noted between requirements for cells to stimulate or to be lysed by CTL, which included (1) the expression of major histocompatibility complex encoded allelic products and (2) the hapten density. Propagation of the CTL within the line required I-A intra-H-2 homology between hapten-treated stimulating cells and the line cells, whereas lytic interaction required H-2K region homology between hapten-treated target cells and CTL. The hapten density requirement was analyzed for a responder (H-2k) and a nonresponder (H-2b) strain to low hapten density modified syngeneic cells. This property was found to be characteristic of the lytic phase rather than of stimulation of CTL. CTL clones could be derived by growing the lines under conditions of limiting dilution in the presence of T cell growth factors. Such clones could not be stimulated by their target antigens and were dependent on T cell growth factors for propagation. Results are discussed in terms of the dependence of development and growth of CTL on T helper cells. (33 Refs)

109. MODIFICATION OF NORMAL HUMAN MYELOPOIESIS BY 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA).

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Blood; 58(6):1119-1126 1981

The tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), induces macrophage characteristics in the HL-60 promyelocytic leukemia cell line. These same cells can be induced to develop mature myeloid characteristics with a variety of other stimuli. Since normal colony-forming units-culture (CFU-C) also have the dual capability of developing colonies with myeloid or monocyte characteristics, the effect of TPA on normal human CFU-C development was studied. To carry out these studies, a method was developed to identify cells histochemically within agar cultures as containing either the myeloid marker, chloroacetate esterase (CAE), or the monocyte marker, nonspecific esterase (NSE). Cells from normal donors were placed into agar cultures with placenta conditioned medium (PCM), TPA in various concentrations, or combinations of PCM and TPA as stimulating materials, and examined after 7-14 days of incubation. TPA alone at concentrations of 5 x 10(-7) M to 10(-9) M stimulated cluster formation. With increasing concentrations of TPA, the percentage of clusters positive for NSE progressively increased, while CAE-positive clusters decreased. In contrast, when TPA at concentrations greater than 10(-9) M was added to PCM, the total number of clusters and colonies decreased. This resulted from a decrease in the number of clusters and colonies that contained the myeloid marker CAE, whereas the number positive for the monocyte marker NSE remained unchanged. These studies demonstrate two effects of TPA on normal CFU-C. In the absence of other sources of colony stimulating activity (CSA), TPA induces clusters. In the presence of PCM, it inhibits the production of myeloid colonies and clusters. Under both conditions, it favors the development of colonies and/or clusters containing predominantly monocytes. (Author abstract) (16 Refs)

110. IN VIVO ACTIVATION OF MACROPHAGES BY CORYNEBACTERIUM PARVUM, PYRAN COPOLYMER AND GLUCAN.

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Int Arch Allergy Appl Immunol; 66(Suppl1):180-182 1981

Three immunopotentiators (IMP) were used to examine whether a high release of prostaglandin E (PGE) from macrophages is a general attribute of activated macrophages or whether it is dissociable from typical functions such as tumor cytotoxicity. Various times after ip injection of C57Bl/6 mice with Corynebacterium parvum (CP; 0.3 mg), pyran copolymer (0.5 mg) or glucan (2 mg), peritoneal macrophages were prepared. PGE was determined by radioimmunoassay. As determined by a tumor cytotoxicity test, all three IMP induced activated macrophages. In spleen, the IMP induced nearly identical increases of macrophages (5 to 20-30%). While all the IMP resulted in a two- to three-fold enhancement of PGE release from spleen cells 1 day after their injection, PGE production after CP reached high levels after 4-16 days. The proliferative response of spleen lymphocytes to Concanavalin A (Con A) stimulation (2.5 ug/ml) was also performed. One day after injection, Con A response of lymphocytes was elevated with all three IMP; however, on following days the only change relative to lymphocytes from unstimulated mice, was a long-lasting suppression due to CP. When PGE synthesis in spleen cell cultures was inhibited by indomethacin, lymphocyte response was competely restored at day 4 after CP injection. Early lymphocyte response (less than 8 days) could be restored by selectively removing strongly-adherent, PGE-producing macrophages by passage over rayon and wool. Such manipulation between days 8 and 16 after CP injection did not alter lymphocyte response. (3 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

111. ULTRASTRUCTURAL LOCALIZATION OF NONSPECIFIC ESTERASE ACTIVITY IN GUINEA PIG AND HUMAN MONOCYTES, MACROPHAGES, AND LYMPHOCYTES.

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Blood; 58(6):1089-1099 1981

Using either hexazotized pararosaniline or new fuchsin as coupling agents, we investigated the ultrastructural localization of alpha-naphthyl acetate esterase (ANAE) activity in guinea pig bone marrow and peritoneal exudates, and in human peripheral blood cells. DFP-inhibitable ANAE activity was present on the cell surfaces of lymphocytes, monocytes, macrophages, neutrophils, eosinophils, basophils, megakaryocytes, platelets, and blasts. Demarcation lines in megakaryocytes and the perinuclear cisternae in normoblasts were also positive. In addition, lymphocytes, monocytes, and macrophages displayed ANAE activity associated with cytoplasmic-vesicle clusters (CVC). Reaction product was always present on the cytoplasmic surfaces of these vesicles and in the adjacent cytoplasm; vesicle interiors were invariably ANAE-negative. Small lymphocytes generally had a single large paranuclear ANAE-positive CVC, whereas mononuclear phagocytes had multiple discrete foci of similar appearing ANAE-positive CVC that sometimes became confluent. ANAE activity was also found in the Gall bodies of human lymphocytes and in coated vesicles of macrophages. Cytoplasmic ANAE activity was increased in oil-induced guinea pig peritoneal macrophages. Both surface and cytoplasmic esterase activities had a neutral pH optimum. An identical distribution of reaction product was observed when alpha-naphthyl butyrate was employed as substrate. The function of these esterases, and their relation to known surface and cytoplasmic neutral proteases, awaits further investigation. (Author abstract) (32 Refs)

112. MACROPHAGE ACTIVATION FOR TUMOR CYTOTOXICITY: CONTROL OF CYTOTOXIC ACTIVITY BY THE TIME INTERVAL EFFECTOR AND TARGET CELLS ARE EXPOSED TO LYMPHOKINES.

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Cell Immunol; 65(1):52-65 1981

Macrophages continuously exposed to lymphokines (LK) and target cells throughout a 48 hr cytotoxicity assay exhibit three-fold more tumoricidal activity than do cells optimally treated with LK before addition of tumor cells. Increased cytotoxic activity induced by continuous LK treatment was not due to direct toxic effects of LK on tumor target cells or to alterations in target cell susceptibility to cytopathic effects of LK-activated macrophages. Moreover, sensitivities of responsive macrophages to LK activation signals and time courses for onset and loss of tumoricidal activity during continuous exposure or LK pulse were identical. Analysis of macrophage or LK dose responses and time courses of development of cytotoxicity each suggest that differences in tumoricidal activity between macrophages continuously exposed or pulsed with LK were quantitative: the number of cytotoxic events was increased 2.7 +-0.2-fold (mean +- SEM for 11 experiments) during continuous LK treatment. Optimal levels of macrophage tumoricidal activity then occur only if effector cells, target cells and activation stimuli are simultaneously present for a defined time interval: tumor cells need not be present during the initial 2 or 3 hr of culture; LK can be removed after 8 hr with little or no loss of cytotoxic activity. However, removal of LK or target cells during the critical 4-to 8-hr interval decreased levels of cytotoxicity three-fold. Thus, nonspecific effector function by LK-activated macrophages is controlled by both the physicochemical nature of the LK mediator and the time interval effector and target cells are exposed to LK. (Author abstract) (20 Refs)

113. A SMALL MOLECULAR WEIGHT PEPTIDE FROM P815 MASTOCYTOMA CELLS INDUCES MACROPHAGE CYTOTOXICITY.

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Immunopharmacology; 3(4):309-316 1981

The mechanism of induction of macrophage cytotoxicity was investigated using P815 mastocytoma cells. Pronase but not RNAase reduced the activity of macrophage inhibitory factor (MIF). UV irradiation did not alter MIF activity, while heating at 100 C for 1 min eliminated it. Supernatants obtained from the TLX9 tumor cell culture after incubation with the mast cell degranulating compound 40/80 were not able to induce macrophage cytotoxicity. Neither an extract prepared from isolated mast cells nor solutions of mass cell product could induce macrophage cytotoxicity against SL2 tumor cells. The MIF in P815 tumor exudates was found to have a molecular wt between 650-700 daltons. Results indicate that the MIF described is not lipid-like, not a virus, and not a mucopolysaccharide. Data support the suggestion that P815 MIF is a small molecular wt peptide. (15 Refs)

114. TUMORICIDAL MACROPHAGES ISOLATED FROM LIVER GRANULOMAS OF SCHISTOSOMA MANSONI-INFECTED MICE.

Loveless SE, Wellhausen SR, Boros DL, Heppner GH
Dept. Immunology, Michigan Cancer Foundation, Detroit, MI, 48201
J Immunol; 128(1):284-288 1982

In murine schistosomiasis, inflammatory macrophages (Mphi) are a major cell type of the granulomata that encase eggs of the tropical helminth Schistosoma mansoni as they are deposited in the liver by adult worm pairs. The granulomatous response is vigorous during acute infection (8 wk) and spontaneously undergoes immunomodulation during chronic infection (20 wk). Inflammatory Mphi isolated from liver granulomas of 8 and 20-wk schistosome-infected CBA/J mice were assessed for their cytolytic potential. Macrophages from vigorous liver granulomas displayed significant cytolytic activity against three mammary tumor lines of strain BALB/cfC3H origin, while leaving untransformed embryo fibroblasts relatively unharmed. The cytolytic activity of inflammatory Mphi from immunomodulated lesions was markedly less than that of cells from vigorous lesions at equivalent effector to target (E:T) cell ratios. Granuloma cell preparations depleted of the inflammatory macrophage component were marginally cytolytic at the higher E:T cell ratio; supernatant fluids from cultured inflammatory Mphi-enriched cell preparations possessed no tumoricidal activity. The cytolytic potential of the vigorous granuloma Mphi was lost subsequent to prolonged in vitro culture. We conclude that inflammatory Mphi in S mansoni egg-elicited granulomas are sufficiently activated to lyse allogeneic tumor cells. The degree of activation appears to correlate directly with the intensity of the granulomatous response. (Author abstract) (53 Refs)

115. 10. POSSIBLE MECHANISMS OF IMMUNOTHERAPY ACTION IN ACUTE NONLYMPHATIC LEUKEMIA: MACROPHAGE PRODUCTION OF COLONY-STIMULATING ACTIVITY.

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Recent Results Cancer Res; 80:64-69 1982

Earlier studies show that immunotherapy (IT) improves prognosis in acute nonlymphatic leukemia (ANLL), and that ANLL cells probably have tumor-associated antigens, for autologous lymphocytes can react to them. Also, IT seems to immunize against allogeneic ANLL cells, but there is no cross-immunity to autologous ones. Moreover, patients immunized against their ANLL cells have no better prognosis than patients not having lymphocytes reacting to their ANLL cells. It has also been suggested that IT causes nonspecific immunostimulation, but IT patients' lymphocytes actually react less than those of patients not given IT. The current hypothesis is macrophage activation: Lymphocyte suppression in IT could be explained by suppressor macrophages. Colony-stimulating activity, produced by bone marrow macrophages, decreases during remission in patients not given IT, but not in IT patients. Numerically, blood cells from patients given IT form more colonies than those from patients not given IT. Three of eight patients given IT had more colonies than the upper normal limit. (Author abstract) (16 Refs)

116. STUDY OF ASIALOGANGLIOSIDES ON SURFACE MEMBRANES OF RAT BONE MARROW CELLS AND MACROPHAGES.

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J Biochem (Tokyo); 90(6):1653-1660 1981

The presence of asialogangliosides on membrane surfaces of rat bone marrow cells and macrophages was studied by an immunological method using anti-glycolipid antibodies with high specificity. The antibodies against N-acetylgalactosaminyl(beta1-4)galactosyl(beta1-4) glucosylceramide (GA2), galactosyl(beta1-3)N-acetylgalactosaminyl-(beta1 4)galactosyl(beta1-4) glucosylceramide (GA1) and fucosyl(alpha1-2)galactosyl(beta1-3)N acetylgalactosaminyl(beta1-4) galactosyl(beta1-4)glucosylceramide (Fuco-GA1) were prepared, and used for cytotoxicity testing and indirect staining by the immunofluorescence technique. In the cytotoxicity test, approximately 40-50% of rat intraperitoneal macrophages were killed by each of the anti-glycolipid antisera. This finding was confirmed by the indirect immunofluorescence staining method with the purified anti-GA2, anti-GA1 and also anti-Fuco-GA1 IgG. When a rat was preimmunized with bovine serum albumin, all macrophages induced in ascites fluid were found to possess GA1 by the staining method. Immature granulocytes were stained specifically with the anti-GA2 antibody. Granulocytes, myelocytes, and megakaryocytes were stained with the anti-GA1 antibody. Blastic myelocytes were stained with the anti-Fuco-GA1 IgG, but lymphocytes were not stained with any of these anti-asialoganglioside antibodies. From these observations, free-type cells such as macrophages and bone marrow cells were found to possess asialogangliosides as membrane components. (Author abstract) (28 Refs)

117. MACROPHAGE ACCUMULATION IN TRANSPLANTED TUMORS IS NOT DEPENDENT ON HOST IMMUNE RESPONSIVENESS OR PRESENCE OF TUMOR-ASSOCIATED REJECTION ANTIGENS.

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Jackson Lab., Bar Harbor, ME, 04609
J Reticuloendothel Soc; 30(5):425-437 1981

The macrophage content of three chemically-induced C57BL/6J sarcomas growing in normal or immunosuppressed mice was assessed to determine whether host immune responsiveness or the presence of tumor-associated rejection Ags was important during monocyte infiltration or macrophage accumulation. Mice were immunosuppressed using various doses of whole body irradiation. Nude mice were also used. The data indicated that there was no relationship between the level of macrophages in a tumor and the ability of the host to mount an immune response or of the tumor to induce one. Moreover, it was apparent that the level of macrophages in a tumor was partly dependent on a critical number of circulating monocytes but not necessarily dependent on a normal blood monocyte count. The data are discussed in terms of possible mechanisms whereby monocytes infiltrate and accumulate in the tumor mass, where they presumably mature into the typical, phagocytic, non-specific, esterase-positive macrophage. (Author abstract) (16 Refs)

118. CHARACTERIZATION OF MONONUCLEAR BLOOD CELL-DERIVED DIFFERENTIATION INDUCING FACTORS FOR THE HUMAN PROMYELOCYTIC LEUKEMIA CELL LINE HL-60.

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JNCI; 67(6):1225-1230 1981

A search was made for physiologically produced differentiation inducing factor(s) (DIF) for the human promyelocytic leukemia cell line HL-60. Mononuclear blood cells, which stimulated with various mitogens, produced DIF, which induced differentiation of HL-60 into phagocytizing nitro blue tetrazolium reducing cells with the morphologic characteristics of granulopoietic or myelomonocytic cells. Induction of differentiation occurred equally well in serum-containing and serum-free media. Protein synthesis was necessary for elaboration of DIF, which seems to be of a protein nature inasmuch as it is destroyed by proteases. Gel chromatography showed that one or two species of DIF with apparent mol wt of 40,000 and 25,000 were produced, depending on the type of mitogen used. At least the 40,000-mol wt DIF was distinct from the colony stimulating activity (CSA), which was produced simultaneously. Our results suggested a role of lymphocytes and/or monocytes for modulation of myelomonocytic hematopoiesis not mediated by CSA. The physiologic importance remains, however, to be demonstrated. (Author abstract) (14 Refs)

119. THE ROLE OF MG++ AND CA++ IN THE DIRECT MACROPHAGE-MEDIATED TUMOR CELL LYSIS.

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FEBS Lett; 135(1):49-52 1981

The role of Ca++ and Mg++ in the direct macrophage-mediated tumor cell lysis was studied with various concentrations of chelating agents, and with media of defined cationic content. Tumor cell DHD K-12 was employed with macrophages which were adherent peritoneal cells from BDIX rats. The macrophage-mediated cytolysis assay involved removal of Ca++ and Mg++ with EDTA, and seeding labeled tumor cells with or without preincubated macrophages. Studies with addition of EDTA and ethylene diamine tetraacetic acid calcium disodium salt (CaEDTA) suggested that macrophage-mediated cytolysis is either inhibited by free Ca++ and/or free Mg++, or enhanced by their complexes with EDTA. Other studies indicated the increased macrophage-mediated cytolysis was not due to diminution of free Ca++ and free Mg++ but could be due to EDTA complexes. Studies with addition of CaEDTA indicated enhancement could be due to the complexes, probably due to CaEDTA. It was found that Mg++ inhibited the tumor cell lysis by BCG-activated macrophages, whereas Ca++ had no effect on cytolysis. These results indicate that the mechanism of direct macrophage-mediated tumor cell lysis could be different from the mechanism of the T lymphocyte-mediated cytolysis. (12 Refs)

120. MACROPHAGES AND METHYLTHIO GROUPS IN LYMPHOCYTE PROLIFERATION.

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J Supramol Struct Cell Biochem; 17(1):11-25 1981

Essential factors for in vitro proliferation of lymphocytic cells and for in vitro function of several immune systems are discussed. Continuous proliferation of many cell lines in vitro, including malignant murine lymphocytes, malignant human plasma cells, malignant human lymphocytes, and murine teratocarcinoma cells, requires addition of a sulfhydryl compound to medium containing fetal calf serum. Sulfhydryl compounds are also known to stimulate normal immune systems in vitro. Methylthio disulfide was found capable of replacing sulfhydryl compounds. Analyses indicated that fetal calf serum contains methyl mercaptan, which may account for its ability to stimulate cell proliferation in contrast to other sera which may not contain methyl mercaptan. When fetal calf serum is dialyzed against glutathione, it loses its ability to support the growth of methyl-thio-dependent cells in the presence of sulfhydryl compounds. Topics discussed include the way macrophages replace methylthio groups, methylthio group generation from methylthioadenosine, methylthio group generation from methylthioadenosine by macrophages and other cells, and the action of methylthio groups in lymphocytic proliferation. (60 Refs)

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY

121. ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY IN HUMAN CANCER: CHARACTERIZATION OF PATIENT LEUKOCYTE ACTIVITY AND TREATMENT EFFECTS.

Hersh EM, Murphy SG, Gutterman JU, Morgan J, Quesada J, Zander A, Stewart D
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Cancer; 49(2):251-260 1982

Antibody-dependent cell-mediated cytotoxicity (ADCC), mediated by peripheral blood Hypaque-Ficoll separated mononuclear cells, was studied in humans using chicken erythrocytes (CRBC) incub ated in a 1:1,200 dilution of rabbit anti-CRBC and human B erythrocytes (HRBC) incubated in a 1:20 dilution of isoantibody. At the optimal target effector ratio of 3:1, ADCC to both CRBC and HRBC was significantly higher than normal in 27 lung cancer, 18 malignant melanoma, and 7 colon cancer patients, but not in 20 breast cancer patients. Chemotherapy (single-agent or combination) in 12 patients did not affect ADCC in vitro but significantly suppressed ADCC to both targets after only 4 or 5 days of therapy in vivo (ADCC to CRBC, 47.4 to 24.1% lysis: ADCC to HRBC, 48.1 to 16.3% lysis). Immunotherapy with intravenous (IV) Corynebacterium parvum or IV methanol extraction residue of BCG (MER) boosted ADCC to both targets within 4 to 7 days of the first dose. It was found that ADCC to HRBC but not to CRBC was completely absent in three cases of active hairy cell leukemia but was present in two cases in remission. The ADCC to HRBC showed an age-dependent increase in both the 51 normal subject and the cancer patients. This was not observed for ADCC to CRBC. The ADCC to CRBC was mediated mainly by an Fc-receptor-positive, nonadherent, small lymphocyte, and ADCC to HRBC was mediated entirely by an adherent monocyte. The ADCC did not correlate significantly with the H3 thymidine incorporation of peripheral blood mononuclear cells, cultured without stimulation for either 1 or 7 days. It also did not correlate with the number of residual granulocytes in the mononuclear cell suspensions. Measurement of ADCC is a useful method of characterizing host defense in malignant disease and its modification by therapy. (Author abstract) (48 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

122. IDENTIFICATION OF T-LYMPHOCYTES AND T-SUBSETS IN HUMAN TONSIL USING MONOCLONAL ANTIBODIES AND THE IMMUNOPEROXIDASE TECHNIC.

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Am J Clin Pathol; 76(6):737-744 1981

A study was performed using monoclonal antibodies and the immunoperoxidase technic to identify T-cells and T-subsets in human tonsil sections. The in situ topographic identification of T-cells, helper cells, and suppressor cells was achieved. This model may therefore be applied to other normal lymphoid tissues. Its potential pathologic importance lies in the fact that certain disorders may be associated with depletion of lymphocyte subsets from their normal areas of 'homing' and that lymphoma cells may mirror their putative normal counterparts in their selective metastatic migration pattern. The improved knowledge of normal lymphocyte subset microenvironment afforded by this technic may therefore be of value in applied pathology. (Author abstract) (46 Refs)

123. RECOGNITION OF POLYMORHPIC H2 DOMAINS BY T LYMPHOCYTES. I. FUNCTIONAL ROLE OF DIFFERENT H-2 DOMAINS FOR THE GENERATION OF ALLOREACTIVE CYTOTOXIC T LYMPHOCYTES AND DETERMINATION OF PRECURSO R FREQUENCIES.

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J Exp Med; 154(6):1717-1731 1981

The fine specificity and receptor repertoire of cytotoxic T lymphocytes (CTL) was examined. Murine histocompatibility complex (H-2) Kk CTL clones were generated in a limiting dilution system and their fine specificity assessed by target inhibition with a panel of monoclonal (mc) anti-H-2Kk antibodies. Poisson distribution analysis yielded three straight lines, indicating the existence of three precursor populations differing in precursor frequency. Av frequency data were 1/400 for CTL I, 1/2,000 for CTL II, and 1/4,000 for CTL III. Limiting dilution curves suggested that the more frequent CTL populations were subject to a suppressive mechanism. Biphasic curves represented CTL I and II in some experiments and CTL II and III in others. Results of target inhibition studies with a panel of mc anti-H-2Kk antibodies that had previously been shown to define two separate clusters of antigenic determinants on the Kk molecule indicated that CTL subsets differ in their receptor repertoire. Application of a single antibody blocked only a fraction of CTL clones, whereas CTL target interaction was totally prevented when numerous epitopes were covered by a mixture of mc antibody or by an alloantiserum. Each antibody exhibited a characteristic inhibition pattern. Thus, each CTL subpopulation appears to consist of various different clonotypes with specificity for different target epitopes. Generation of CTL subpopulations with specificity for particular domains may be controlled by suppressive mechanisms. The data suggest that CTL recognize basically the same polymorphic domains on the H-2Kk molecule defined by antibodies; regulatory mechanisms apparently determine the expressed repertoire in CTL populations. (25 Refs)

124. METHOTREXATE RESCUE BY 5-METHYLTETRAHYDROFOLATE OR 5-FORMYLTETRAHYDROFOLATE IN LYMPHOBLAST CELL LINES.

Dudman NP, Slowiaczek P, Tattersall MH
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Cancer Res; 42(2):502-507 1982

The rescue of lymphocytes from methotrexate (MTX) growth inhibition by 5-methyltetrahydrofolate (5-methyl-THF) and 5-formyltetrahydrofolate (5-formyl-THF) has been studied. Rescue by 5-methyl-THF is selective for cells with high levels of homocysteine:5-methyl-THF methyl-transferase (methyltransferase). At MTX concentrations which inhibited growth greater than or equal to 85% in both leukemic T-lymphocytes (CCRF-CEM) and Epstein-Barr-transformed B-lymphocytes (LAZ-007), 5 uM 5-formyl-THF rescued more effectively than did 5-methyl-THF, in either the presence or absence of the methyltransferase inhibitor, nitrous oxide. At less inhibitory MTX concentrations, both reduced folates rescued equally, except when methyltransferase was inhibited by nitrous oxide in which case 5-formyl-THF was clearly superior. In the absence of nitrous oxide, both cell lines contained approx equal amounts of methyltransferase. Some apparent differences in the rescue of these cell lines with 5-methyl-THF were attributable to their different sensitivity to MTX. When metabolism of reduced folates was severely impaired by MTX and nitrous oxide, lymphocytes were rescued with 5-[methyl-14C]methyl-THF, and the uptake of 14C into DNA was measured. Incorporation was very low, indicating that cellular oxidation of 5-methyl-THF to 5,10-methylene-tetrahydrofolate is minimal even under forcing conditions. MTX selectivity in vivo will be influenced by the level of methyltransferase in tumor and normal tissues. (Author abstract) (21 Refs)

125. FUNCTIONAL PROPERTIES OF CONTINUOUSLY CULTURED HUMAN T LYMPHOCYTES.

Boylston AW, Anderson RL, Haworth CA
Dept. Experimental Pathology, St. Mary's Hosp. Medical Sch., London W2 1PG, England
Clin Exp Immunol; 43(2):329-335 1981

Properties of human T lymphocytes (CCTC) maintained in continuous culture by a new method were studied. CCTC did not proliferate in response to phytohemagglutinin, concanavalin A, or allogeneic lymphocytes. CCTC inhibited proliferation of normal cells in mixed lymphocyte culture and were cytotoxic to a number of human lymphoid cell lines. Properties of CCTC differed significantly from those of cells grown on T-cell growth factor. (16 Refs)

126. ESTABLISHMENT OF HUMAN T LYMPHOCYTE CLONES HIGHLY CYTOTOXIC FOR AN EBV-TRANSFORMED B CELL LINE IN SERUM-FREE MEDIUM: ISOLATION OF CLONES THAT DIFFER IN PHENOTYPE AND SPECIFICITY.

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J Immunol; 128(1):95-99 1982

A human T cell culture (HLA A2; w23 B40; W44 Cw4) was established by repetitive stimulation with an Epstein Barr virus-transformed B cell line JY in a serum-free culture medium. This T cell culture was highly cytotoxic for JY but had negligible nonspecific natural killer cell-like activity against the myeloid cell line K562. Cloning by limiting dilution procedures in serum-free medium resulted in a high plating efficiency and the establishment of a large number of cytotoxic clones. Three of these clones (31, 38, and 77) were selected. Phenotypic characterization by using a series of monoclonal antibodies and fluorescein isothiocyanate-labeled goat anti-mouse immunoglobulin revealed that clone 31 was OKT 3+, 4-, T8+, Ia+, OKM 1-, whereas clone 38 was OKT 3+, 4+, T8-, Ia+, and OKM 1-, indicating that cytotoxic T cells are not restricted to the T8+ subset and can reside in the OKT 4+ 'inducer/helper' T cell subset. Because the cytotoxic reaction of clone 31 was inhibited by a monoclonal antiserum that recognizes all HLA A, B, and C specificities, whereas that of clone 38 was not blocked, it was concluded that in contrast to clone 38, clone 31 recognized HLA A, B, or C antigens. A preliminary analysis indicated that clone 31 reacted with HLA B7. The specificity of clone 38 remained unclear. The cytotoxic reaction of the T8+ clone 31 was blocked by anti-T8, a monoclonal antibody specific for human cytotoxic/suppressor T cells, suggesting that the T8 determinant plays a role in the cytotoxic process. The cytotoxic reaction of the T8-clone 38 was not blocked by anti-T8. The third clone (77), which was OKT 3+, 4-, T8+, Ia+, and OKM 1-, was cytotoxic only in the presence of minimal concentrations of lectin. Our results indicate that stable cytotoxic T cell clones can be established successfully in serum-free medium. (Author abstract) (26 Refs)

127. DURING LYMPHATIC REGENERATION PRECURSORS FOR MAJOR HISTOCOMPATIBILITY COMPLEX-RESTRICTED CYTOTOXIC T CELLS APPEAR BEFORE ALLOREACTIVE PRECURSORS.

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J Exp Med; 155(1):327-332 1982

A sublethal dose of cyclophosphamide (CY) was injected into mice; the appearance of the capacity of the regenerating spleen to form cytotoxic T lymphocytes (CTL) in response against 2,4,6 trinitrophenyl-coupled syngeneic cells or against allogeneic cells was examined. Specific CTL-responses were found only to 2,4,6 trinitrophenyl-coupled cells 8 days after CY injection. A low alloresponse was first observable 2 wk after CY injection. (16 Refs)

128. IN VITRO CELLULAR REGULATION OF MONOCYTE FUNCTION: EVIDENCE FOR A RADIOSENSITIVE SUPPRESSOR.

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J Reticuloendothel Soc; 30(5):373-379 1981

Radiation was used in the following studies to better define and understand the interaction between human killer monocytes and their suppressor lymphocytes in a cytotoxic assay. Human mononuclear leukocytes become spontaneously cytotoxic to a variety of red blood cell targets after 7 days of in vitro culture. This phenomenon was independent of exogenous stimulus by Ag, Ab, or mitogen. Monocytes appeared to be the cytotoxic cell and were controlled by lymphocyte suppressor cells. In the present study, x-irradiation enhanced the magnitude of monocyte-mediated cytotoxicity generated and stimulated an earlier appearance of this cytotoxicity when compared with that of unirradiated mononuclear leukocytes. The effect of x-irradiation (150 to 600 R) on separated populations of mononuclear leukocytes enriched for either lymphocytes or monocytes was examined; this enhanced cytotoxicity appeared to be secondary to inactivation of the lymphocyte suppressor cells. (Author abstract) (11 Refs)

129. CYTOTOXIC T LYMPHOCYTES INDUCED BY SYNGENEIC MOUSE MELANOMA CELLS RECOGNIZE HUMAN MELANOMAS.

Wakabayashi S, Taniguchi M, Tokuhisa T, Tomioka H, Okamoto S
Dept. Dermatology, Sch. Medicine, Chiba Univ., Chiba, Japan
Nature; 294(5843):748-750 1981

Cytotoxic T lymphocytes (CTLs) against syngeneic B16 melanoma cells were induced in C57BL/6 mouse spleen cells cultured with mitomycin C-treated B16 cells. The CTLs killed cells of four human melanoma cell lines in addition to the syngeneic melanoma cells; the CTLs did not affect other mouse or human tumors. The T cells appeared to recognize melanoma-specific antigens rather than interspecies determinants of the major histocompatibility complex. C57BL/6 mice do not express I-E/I-C subregion gene products of the mouse H-2 complex that share cross-reactive determinants with human HLA-DR antigens. (14 Refs)

130. FUNCTIONAL CHARACTERIZATION OF T-LYMPHOCYTES GROWN IN SEMISOLID AGAR (MEETING ABSTRACT).

Ludwig C, Forster HK, Troxler M, Ludwig R, Obrecht JP
Division of Oncology Department for Clinical Investigation, Basle, Switzerland
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Phytohemagglutinin (PHA) stimulated peripheral blood T-cells grown for 6 days in agar (TPH-agar) were assayed for their capacity to induce polyclonal pokeweed mitogen (PWM) dependent B-cell differentiation. In the same system we investigated the inductive capacity of fresh peripheral blood T-cells and their subpopulations, TM and TG. Differentiation of peripheral blood B-lymphocytes to plasma cells in the assay system was demonstrated by the appearance of cells containing intracytoplasmic immunoglobulines detectable by a direct immunofluorescence method on fixed cells. Total T-cells and the subpopulation TM were found to exhibit helper activity, whereas TG cells showed suppressor activity. The PHA-stimulated-T-cell population harvested from agar differentiation capacity. Low TPHA-agar-cell concentrations resulted in helper activity, increasing TPHA-agar cell concentrations caused a change to suppression of B-cell differentiation. The suppressor effect can be abolished by irradiation of TPHA-agar-cells. PHA-stimulation in agar cultures obviously favors the growth of irradiation sensitive T-cells mediating suppressor activity. (no Refs)

131. STIMULATORY ACTIVITY FOR HUMAN PLURIPOTENT HEMOPOIETIC PROGENITORS PRODUCED BY A HUMAN T-LYMPHOCYTE CELL LINE.

Fauser AA, Messner HA, Lusis AJ, Golde DW
(c/o Messner) Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ont. M4X 1K9, Canada
Stem Cells; 1(2):73-80 1981

A human T-cell line (Mo) constitutively produces stimulatory activities for human pluripotent stem cells. Nine bone marrow samples from eight individuals were cultured with 5%

phytohemagglutinin-stimulated leukocytes (PHA-LCM) or 5% Mo-conditioned medium (Mo CM) obtained from various passages. Three bone marrow specimens were cultured with partially purified erythroid-potentiating activity (EPA). The frequency of mixed colonies observed with various Mo CM preparations was almost always higher than the frequency observed from PHA-LCM. The cellular composition of mixed colonies grown with PHA-LCM varied from that seen with Mo CM. Mixed colonies grown in the presence of Mo CM developed a large eosinophilic component in addition to a small number of neutrophils and a larger number of erythroblasts. Megakaryocytes were not observed in colonies grown with Mo CM. The size of colonies grown in the presence of Mo CM was smaller than the size observed with PHA-LCM. Erythroid burst formation was at best increased to levels obtained with PHA-LCM, while the planting efficiency of target cells (CFU-C) was consistently higher with crude Mo CM preparation. No differences were observed comparing the stimulatory effect of the original material with the boiled preparations, indicating that these stimulatory activities are quite heat stable. A similar requirement for erythropoietin was observed in cultures stimulated by crude or purified Mo CM or PHA-LCM. The most potent stimulator of mixed colonies tested was a preparation of EPA partially purified from Mo CM. (22 Refs)

132. CLONE SIZE POTENTIAL AND SENSITIVITY TO COLONY-STIMULATING ACTIVITY: DIFFERENTIATION-LINKED PROPERTIES OF GRANULOCYTE-MACROPHAGE PROGENITOR CELLS.

Francis GE, Berney JJ, Bodger MP, Bol SJ, Wing MA, Hoffbrand AV
Dept. Haematology, The Royal Free Hosp., Pond St., Hampstead, London NW3 2QG, England
Stem Cells; 1(2):124-139 1981

Clone size potential and sensitivity to the specific granulocyte-macrophage regulator colony-stimulating activity (CSA) were studied. Properties of normal granulocyte-monocyte progenitor cells and the difference in linked properties were investigated. The results show that clone size potential and sensitivity to CSA are properties of granulocyte-macrophage clone-forming cells linked in an organized fashion. Four different techniques were used to minimize the possibility of obtaining apparent linking of the two properties merely due to production of artefacts during the separation procedure or to co-purification of CSA-resistant cells with a different population which have large clone size potential. Bone marrow cells from normal donors were used. The techniques enabled the use of clonogenic cells with different equilibrium density centrifugation, adherence to microcarrier beads, osmotic lysis, and fluorescence-activated cell sorting. Mean clone size is directly related to the amount of CSA required to stimulate 50% of the cells to clone formation. Results showed that the linking of clone size potential and sensitivity to CSA is not confined to acute myeloid leukemia clonogenic cells since it occurred within normal granulocyte-monocyte progenitor populations. The differences in the two properties reflect the position of the normal progenitors in the granulocyte-monocyte maturation hierarchy. (21 Refs)

133. MONOCLONAL ANTIBODY AGAINST A1 LEWIS D ANTIGEN PRODUCED BY THE HYBRIDOMA IMMUNIZED WITH A PULMONARY CARCINOMA.

Iwaki Y, Kasai M, Terasaki PI, Bernoco D, Park MS, Cicciarelli J, Heintz R, Saxton RE, Burk MW, Morton DL
Dept. Surgery, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Cancer Res; 42(2):409-411 1982

A monoclonal antibody (CALed) against a human pulmonary squamous cell carcinoma line was cytotoxic to the line but did not react to an autologous B-lymphoblastoid line. Although the antibody was thought to be cancer specific, principally on the basis of this evidence, the antibody actually had the A1 Lewis d (Led) specificity. It reacted with approximately 2% of the random donor T-lymphocytes and with all six lymphocytes from donors who were A1 Led type without reacting to lymphocytes of any other type. The monoclonal antibody reactivity was also absorbed out by A1 Led red blood cells but not by red cells of other types. We conclude that the A1 Led antigen had been synthesized by the pulmonary carcinoma lines but not by the autologous lymphoblastoid line, resulting in disparity for this antigen. Since the combination A1 Led only occurs in 2% of the population, it is difficult to distinguish this type of antibody from tumor-specific antibodies. (Author abstract) (14 Refs)

CMI METHODOLOGY

134. STAINING OF GRANULOCYTIC CELLS BY CHLORAZOL BLACK E.

Kass L
Dept. Pathology, Cleveland Metropolitan General Hosp., 3395 Scranton Road, Cleveland, OH, 44109
Am J Clin Pathol; 76(6):810-812 1981

Using the trisazo dye Chlorozol black E, granules in neutrophilic granulocytes stained pale orange, gray and black. In promyelocytes, granules were mainly orange, whereas in myelocytes and metamyelocytes, mixtures of orange and black granules were seen. In neutrophils, a few orange granules were seen, and most of the granules stained gray and black. In eosinophils and basophils, granules stained orange. In monocytes, a few black and gray staining granules were seen. In lymphocytes, as well as other marrow cells like erythroblasts and megakaryocytes, granules were not visualized. Chlorazol black E may be a useful addition to the cytochemistry of blood cells, particularly in distinguishing cells of granulocytic origin from other cell types. (Author abstract) (12 Refs)

135. THE USE OF MODIFIED CUNNINGHAM CHAMBERS FOR THE ENUMERATION OF H ROSETTES, E ROSETTES, AND LYMPHOCYTE-TUMOR CELL CONJUGATES.

Pross HF, Gallinger LA, Rubin P, Baines MG
Ontario Cancer Foundation, Kingston Clinic, King Street West, Kingston, Ontario K2L 2V7, Canada
Int Arch Allergy Appl Immunol; 66(4):365-371 1981

In this paper, we have described the use of a slide-coverslip Cunningham chamber which is ideal for counting delicate rosettes and lymphocyte-tumor cell conjugates. The ease of construction, facility of use, and economy of cost in comparison with hemocytometers make the use of these chambers the method of choice for rosette counts in general. In contrast to standard double-slide Cunningham chambers, the design of these rosette chambers is such that they can be used with ordinary light microscope objectives (including oil immersion), they can be more easily loaded without trapping air bubbles, and they can be sealed without tilting the slide. As an example of one potential application of these chambers to tumor immunology, data have been presented showing the high proportion of lymphocyte-tumor cell conjugates which can be formed by human peripheral blood cells. The ability of any particular tumor cell to form conjugates did not necessarily reflect the susceptibility of that cell type to natural killer (NK) cell-mediated lysis, nor was there any evidence that E rosette-forming cells preferentially formed conjugate in comparison to non E rosette-forming cells. (Author abstract) (12 Refs)

136. DEVELOPMENT OF IN VITRO ASSAYS FOR MYELOMA COLONY FORMING CELLS (MEETING ABSTRACT).

Hamburger AW
American Type Culture Collection, Rockville, MD, 20852
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussells, Belgium European Organization for Research on Treatment of Cancer; :A19 1981

This presentation summarizes the development of in vitro assays which permits formation of colonies of human monoclonal plasma cells in semi-solid media. The assay developed at the University of Arizona can be described as follows. Colony growth was induced with either 0.02ml of human RBC or 0.25ml of medium conditioned by the adherent spleen cells of mineral oil primed Balb/c mice. After 2-3 wk in culture, up to 500 colonies appeared, yielding a max plating efficiency of 0.1%. The number of myeloma colonies formed as proportional to the number of cells plated between concentrations of 10(5) to 10(6). Morphological, histochemical, and functional criteria showed that colonies consisted of immature plasmablasts and mature plasma cells. This assay was used to define a number of biophysical and immunological properties of the myeloma colony forming cells (MCFCS). Attempts have also been made to develop a monoclonal antibody against plasma cell antigens and to test its effect of MCFCs. Due to variability of the conditioned media in supporting myeloma colony growth, other investigators have devised alternative c ulture methods for MCFCs. The method described by Izaguirre depends on 1) exhaustively depleting cell suspensions of T lymphocytes, 2) a medium conditioned by T lymphocytes in the presence of phytohemagglutinin (PHA) and 3) irradiated autologous or homologous T lymphocytes. Plating efficiencies were increased up to 1-2% by this method. Ludwig and Swetly also devised a method for cloning myeloma cells in plasma clot cultures and assessed the effect of interferon on cells from 17 patients. The specific factors that support the growth of MCFCs in these systems are unknown. The assay for MCFCs correctly predicted clinically meaningful drug sensitivity with 79% accuracy and resistance with 95% accuracy for a number of myeloma patients. (no Refs)

137. NON-FROZEN PRESERVATION OF COMMITTED HEMATOPOIETIC STEM CELLS FROM NORMAL HUMAN BONE MARROW.

Kohsaki M, Yanes B, Ungerleider JS, Murphy MJ
The Bob Hipple Lab. for Cancer Res., Wright State Univ. Sch. Medicine, 3525 Southern Blvd., Dayton, OH, 45429
Stem Cells; 1(2):111-123 1981

Optimal conditions were examined for maintaining normal human hematopoietic stem cells without cryopreservation. Studied were the effects of serum, N-2-hydroxyethyl-piperadine-N'-ethanesulfonic acid (HEPES), citrate-phosphate-dextrose (CPD), and storage temperature. The erythroid bursts colony (BFU-e) formation technique was used in addition to CFU-e (the 'late' erythroid stem cell) and granulocyte/macrophage precursor stem cells (CFU-c). HEPES was used to maintain the hydrogen concentration (pH) of the storage medium between 7.3-7.5. The addition of CPD was useful for helping to neutralize the pH. Stem cell integrity (CFu-c, CFu-e, and BFu-e) was optimally maintained when the bone marrow cells were suspended in a medium containing 40% fetal calf serum, 25 milliM HEPES, and 12.28% CPD and maintained at 4 C. Under this storage conditions the recovery of functionally intact early erythroid stem cells BFU-e was 84% after 2 days, 44% after 4 days, and 12% after 7 days. 'Monocytoid' cells tended to increase in number in the samples kept at 24 C. The actual number of lymphocytes remained constant. The alterations in the cells during the storage could not be detected from the available data. Results indicate that non-frozen short-term storage of human bone marrow may be of clinical utility in bone marrow transplantation. (29 Refs)

138. PHAGOCYTOSIS: FLOW CYTOMETRIC QUANTITATION WITH FLUORESCENT MICROSPHERES.

Steinkamp JA, Wilson JS, Saunders GC, Stewart CC
Los Alamos Natl. Lab., Los Alamos, NM, 87545
Science; 215(4528):64-66 1982

The phagocytosis of uniform fluorescent latex particles by pulmonary macrophages in the rat was analyzed by flow cytometric methods. The percentage of phagocytic macrophages and the number of particles cell per were determined from cell-size and fluorescence histograms. A comparison of in vivo and in vitro phagocytosis data showed that the percentage of phagocytic lavaged macrophages reflected the availability of instilled particles. With sodium azide used to model phagocytosis inhibition, it was shown that the percentage of phagocytic cells and the number of particles per cell can be determined simultaneously. (Author abstract) (9 Refs)

139. DETECTION OF TERMINAL TRANSFERASE IN PARAFFIN SECTIONS WITH THE IMMUNOPEROXIDASE TECHNIQUE.

Halverson CA, Falini B, Taylor CR, Parker JW
Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA
Am J Pathol; 105(3):241-254 1981

Terminal deoxynucleotidyl transferase (TdT) is an early T-cell differentiation marker in a number of species, including man. We have demonstrated TdT in the nuclei of cortical thymocytes in paraffin-embedded sections of calf, rat, and human thymus by indirect immunoperoxidase techniques. In addition, these techniques have been used to verify and extend enzyme assay results by detecting TdT in blast cells from 10 patients with convoluted T-cell lymphoma/leukemia, 1 patient with acute granulocytic leukemia, 1 patient with chronic granulocytic leukemia in blast crisis, and 1 patient with non-T non-B acute lymphocytic leukemia. (Author abstract) (49 Refs)

140. A RAPID NEW METHOD OF MEASURING PHAGOCYTOSIS AND CYTOTOXICITY IN MACROPHAGE TISSUE CULTURES.

Friedrich EA, Glinorz R
German Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
J Immunol Methods; 47(2):259-262 1981

The compound 111Indium as a radioactive tracer for labelling cells has advantages of 51chromium: very low leakage afer 24 h, superior counting properties of the radionuclide 111indium, and a labeling yield of greater than 70%. Tissue culture chamber slides combine the advantage of tissue culture micromethods with simple preparation techniques used in histology. We report here results with peritoneal macrophages as effector cells and erythrocytes and tumor cells as targets. Phagocytosis and cytotoxicity were measured easily and rapidly. (Author abstract) (8 Refs)

SUPPRESSOR CELL ACTIVITY

141. GENERATION OF SUPPRESSOR CELLS FOR NATURAL KILLER (NK) ACTIVITY IN CANCER PATIENTS AFTER SURGERY (MEETING ABSTRACT).

Uchida A, Micksche M
Institute for Cancer Research, University of Vienna, Vienna, Austria
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Surgery often results in immunodeficiency and influences the incidence of metastases. NK cells seem to be important in host resistance against circulating tumor cells and therefore able to prevent the development of metastases. We are the first to demonstrate that human NK activity is regulated by suppressor monocytes in carcinomatous pleural effusion. We report here the effects of surgery on NK activity and its regulatory mechanisms in cancer patients. NK activity against K562 cells determined in a 4-hr chromium release assay of preoperative patients was comparable to that of normal donors. After surgery, NK activity of blood mononuclear markedly decreased, whereas lymphoproliferative response did not. Sephadex G 10 column passage of postoperative mononuclear cells gave no increase in cytotoxicity. When these monocyte-depleted cells were further cultured for 24 hr, they showed a significant increase in NK activity. Futhermore, NK activity of normal lymphocytes was suppressed by postoperative monocytes, while mitogenic response was not. This suppression of NK activity required 24 hr preculture of suppressor monocytes and NK effector cells but not the presence of monocytes in the cytotoxicity assay. Neither postoperative sera nor culture supernatants of postoperative monocytes were suppressive for NK cells. In addition, prostaglandins were not involved in monocyte-mediated suppression of NK cells. Immunotherapy with OK-432 was able to prevent reduction of NK activity and generation of NK suppressor cells after surgery. These results suggest that the appearance of suppressor monocytes in the circulation could be one cause of the depression of NK activity in cancer patients following surgery and this may be an indication to start with immunotherapy in the preoperative phase. (no Refs)

142. SUPPRESSOR CELL ACTIVITY OF FERRITIN-BEARING LYMPHOCYTES IN PATIENTS WITH BREAST CANCER.

Moroz C, Kupfer B
Rogoff-Wellcome Medical Res. Inst., Beilinson Medical Center, 49100 Petah Tikva, Israel
Isr J Med Sci; 17(9/10):879-881 1981

In patients with early stages (I, II) of breast cancer we identified a subset of circulating lymphocytes that carry ferritin on their surface. No such lymphocytes were identified in normal women nor in women with benign breast disease. These cells did not form spontaneous rosettes with sheep red blood cells. Further studies revealed that in vitro treatment of the patients' lymphocytes with levamisole resulted in the removal of the surface ferritin and in an increase in the reactivity of the lymphocytes in mixed lymphocyte culture (MLC). Separation of the ferritin-positive lymphocytes from the E-rosetting T cells resulted in an increased reactivity of the patients' T cells in MLC. Readdition of the fraction containing the ferritin-positive cells to a mixed lymphocyte culture resulted in a decrease in the proliferative response of the patients' T lymphocytes. It is suggested that the ferritin-positive lymphocytes in breast cancer patients represent an active suppressor cell subset. (Author abstract) (13 Refs)

143. EFFECT OF ADJUVANT THERAPY ON SUPPRESSOR SYSTEMS IN PATIENTS WITH COLORECTAL CANCER (MEETING ABSTRACT).

Robinson E, Mekori T, Segal R
Department of Oncology, RAMBAM Medical Center, Technion, Haifa, Israel
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Two suppressor systems were studied in 34 healthy donors and 18 patients with colorectal cancer Duke's B2 and C, by T-lymphocyte proliferation. The level of suppression in the induced suppressor system (ISS) was determined by the ratio of Thymidine incorporation by cells stimulated by suboptimal doses of Concanavalin A, 24 hr after incubation to the counts of cells stimulated at 0 time. Before therapy the number of tests expressing suppression or helper effect and their level was similar in patients and healthy controls. The patients were randomized after surgery into 2 groups, one being treated by radio-chemotherapy and the second by radio-chemotherapy and methanol extraction residue of BCG (MER). After chemoradiotherapy the level of suppression level decreased while the increased and the level of the helper effect decreased. After chemo-radiotherapy + MER the number of tests showing suppression and their level decreased while the level of helper effect increased. The adherent cell suppressor system (ACSS) was tested by removal of the adherent cells on plastic petri dishes. The level of suppression was determined by the ratio of total lymphocyte proliferation to the proliferation of nonadherent cells. In patients with colorectal cancer the level of helper effect and suppression was higher compared to the controls. After treatment the number of tests showing helper effect as well as the level decreased. This was more pronounced in the radio-chemotherapy MER group compared to the radio-chemotherapy group. These results will be discussed in view of the results of a previous study showing a longer survival and disease-free interval in patients treated by chemo-radiotherapy + MER compared to those treated by chemo-radiotherapy alone. (no Refs)

OTHER RELATED STUDIES

144. OBTENTION OF 7 ASCITES TUMOR LINES EXPRESSING H-2S AND NOT H-2K FROM A C3H-SPECIFIC POLYOMA-INDUCED SOLID TUMOR.

Robert F, Oth D, Berebbi M
INSERM-U.95, Plateau de Brabois, 54500 Vandoeuvre, France
Transplant Proc; 13(4):1828-1832 1981

A tumor system where antigenic gains and losses were observed in seven different ascitic sublines derived from the same original solid form tumor is presented. The tumor was produced in vitro by infection of C3H embryo cells with polyoma virus (small plaque). The solid form is C3H-specific and is identified as BROC-S. The solid BROC-S and three of the ascitic lines were grafted to untreated and to A.SW immunized syngeneic recipients. The three ascitic lines were totally inhibited in C3H hosts immunized with either splenic or skin tissues. The solid BROC-S form was not inhibited. Results suggests the presence of A.SW-like antigens in the ascitic lines. The ascitic line BROC-A1 and other ascitic lines are sensitive to antiserum obtained by C3H anti-A.SW tissue immunization. The ascitic lines apparently contain A.SW-like antigens detectable by serology. Cell-mediated lymphocytotoxicity (CML) was determined using cytotoxic T lymphocytes obtained from C3H mice sensitized against A.SW spleen cells. BROC-A1 was lysed by anti-A.SW, but BROC-S was not. Spleen cells from A.SW mice immunized against C3H splenocytes were tested for cytotoxic activity against the tumor cells. The BROC-S line and C3H-Con-A blasts were killed; the ascitic form was not lysed. Both serologic and CML data are compatible with the view that the ascitic lines have been converted from a C3H line towards an A.SW-like line. BROC-S contains the fast form of glucose phosphate isomerase. BROC-A1 ascites contain both fast and slow forms of the enzyme when harvested from a mouse but only the slow form (like A.SW tissue) when harvested from culture. (6 Refs)

145. BIOCHEMICAL ACTIVITIES OF LYSOSOMAL ACID HYDROLASES IN LEUKEMIC CELLS.

Tanaka T, Kobayashi M, Saito O, Kamada N, Kuramoto A, Usui T
Dept. Pediatrics, Hiroshima Univ. Sch. Medicine, Hiroshima, 734, Japan
Clin Chim Acta; 117(2):121-131 1981

The biochemical activities of eight lysosomal hydrolases were determined in various types of leukemic cells with 4-methylumbelliferyl compounds. Among the hydrolases, characteristic alterations were found with alpha-mannosidase (a-MAN), beta-galactosidase (b-GAL), and N-acetyl-beta-glucosaminidase (NABG) in cells from 48 patients with different types of leukemia. a-MAN was markedly higher in various myelogenous leukemia (acute myelogenous leukemia, acute monocytic leukemia [AMoL], acute myelomonocytic leukemia [AMMoL], chronic myelogenous leukemia [CML], and chronic myelomonocytic leukemia [CMMoL]) than in lymphogenous leukemias (acute lymphogenous leukemia, T-cell leukemia, hairy cell leukemia, and chronic lymphogenous leukemia) without exception. b-GAL activity also showed differences between lymphogenous and myelo(mono)genous leukemia with the exception of T-cell leukemia. NABG activity in myelo(mono)genous leukemic cells was above the range of normal granulocytes. The changes in the enzyme levels were consistent. The lymphocytic or myelocytic nature of three cases of acute undifferentiated leukemia could be determined by these enzyme studies. The enzymatic abnormalities were also found in morphologically mature neutrophils from patients with not only chronic types (CML, CMMoL), but also in acute types (AMoL, AMMoL) of leukemia, and were similar to the enzymic abnormalities of the respective leukemic cells. Also described are the activities of beta-glucuronidase, alpha-galactosidase, alpha-fucosidase, acid phosphatase, and aryl sulfatase. Analysis of lysosomal enzymes may be valuable in the differentiation of leukemias. (24 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/118

AUTHOR INDEX WITH CITATION NUMBERS

Abe I 15
Abrahm JL 109
Ahrlund-Richter 99
Akagi T 74
Akwari AM 8
Albert F 108
Amagasaki T 18
Anderson RL 125
Anderson TC 17
Andersson B 115
Arai S 102
Ashman RF 83
Azuma I 49
Baccarani M 10
Bach FH 100
Bagnara G 10
Baines MG 135
Ballatori E 43
Bang B 127
Barcos M 3
Barg S 2
Barlin E 110
Basten A 86
Belotti O 71
Bennink JR 97
Beran M 115
Berebbi M 144
Berney JJ 132
Berney JJ 7
Bernoco D 133
Bernshtein MI 19
Betzler M 6
Billing R 83
Binden C 91
Bland PW 22
Blau HJ 38
Blom J 29
Boccadoro M 31
Bodger MP 132
Bol SJ 132
Bonavida B 101
Bonavida B 98
Bonnard 96
Bonnard 98
Bonnard GD 36
Bonnard GD 68
Boraschi D 55
Boros DL 114
Bose HR 69
Boutwell RK 85
Boylston AW 125
Bracaglia AM 43
Britton DC 22
Bruley-Rosset M 88
Brunelli M 10
Buferne M 108
Burk MW 133
Cannon GB 29
Catalona WJ 41
Cernetti C 43
Chan G 83
Chan JK 8
Chan S 40
Chang KJ 45
Chang-xue Z 50
Check IJ 27
Chiba Y 15
Chirigos MA 52
Cho BC 46
Chudomel V 70
Cicciarelli J 133
Cohen N 66
Cohen SD 107
Colmerauer ME 93
Colvin M 95
Connor R 29
Cooper RA 13
Corte G 82
Cossu G 13
Cowens JW 95
Cupissol D 28
Cupissol D 5
Daddona PE 42
Dadey B 3
Danilova TS 25
Davis S 43
De Fabo EC 63
De Vries JE 126
DeMeester TR 27
Decker JM 128
Deimann W 110
Den Otter W 113
Deveric G 30
Doherty PC 97
Dohy H 65
Dokhelar MC 75
Dudman NP 124
Dullens HF 113
Dutton RW 96
Dvorak AM 111
Dvorak HF 111
Edwards A 91
Eggers G 38
Eidlen DM 117
Evans R 117
Everett MA 122
Falini B 139
Fan J 101
Fauser AA 131
Favier F 5
Feldman M 105
Felix E 37
Ferrone S 100
Festenstein H 64
Finale Y 75
Finke JH 98
Flad HD 6
Florentin I 88
Folds JD 8
Fopp M 89
Forster HK 130
Francis GE 132
Francis GE 7
Frid IA 19
Friedrich EA 140
Fujimoto S 21
Fukushima M 93
Fuyama S 102
Gallinger LA 135
Garrido F 98
Geisenhainer U 6
Gemsa D 110
Gidlund M 76
Gillis S 100
Giraudo Conesa 44
Gladkova NE 106
Glinorz R 140
Gobbi M 10
Golde DW 131
Golde DW 83
Golomb HM 27
Good RA 87
Gorelik E 61
Goronzy J 123
Gorsky T 94
Gorsky Y 94
Goutner A 88
Grefft-Alami A 48
Griffith K 17
Grogan E 81
Grulich M 38
Guerci O 71
Guimezanes A 108
Gupta S 87
Gutterman JU 121
Halverson CA 139
Hamburger AW 136
Hammerling GJ 123
Han T 3
Haworth CA 125
Hayward AR 78
Heacock EH 50
Heintz R 133
Henderson ES 3
Heppner GH 114
Herberman RB 29
Herberman RB 61
Herfarth C 6
Hersey P 91
Hersh EM 121
Heston WD 41
Hizuta A 60
Hockley AB 35
Hoelzer JD 69
Hoffbrand AV 132
Hoffbrand AV 7
Hoffman GC 4
Holmes JM 58
Hoshino T 16
Hozumi M 49
Hrsak I 30
Hsieh KH 45
Hunter RL 27
Hurme M 127
Ihle JN 53
Ijssel H 126
Ikeda S 18
Imamura N 65

Isakov N 105
Israel L 48
Ivanyi P 98
Iwaki Y 133
Izumi A 80
Janot C 71
Jeannin JF 119
Jelliffe DB 34
Jelliffe EF 34
Jones EH 35
Jones SE 17
Kamada N 145
Kamada R 116
Kamihira S 18
Kanayama H 80
Kane RG 92
Karrison T 27
Kasai M 133
Kass L 134
Katz S 37
Kaur P 87
Kawamura S 15
Kharchenko VP 25
Khomchenovskii 106
Kim SJ 46
Kimura N 24
Kinoshita K 18
Kireeva IV 106
Kitagawa N 39
Kitamura T 18
Kiyohashi A 104
Klein E 94
Klein E 99
Kleinerman ES 128
Kobayashi M 145
Koga S 80
Kohsaki M 137
Kojima K 116
Kokoschka EM 90
Komatsu S 24
Korngold R 97
Koziol JA 93
Kripke ML 63
Kruse H 38
Krusic J 30
Kubonishi I 74
Kuentz M 23
Kumar RK 59
Kuo AL 13
Kupfer B 142
Kuramoto A 145
Lauber Ch 89
Lawler SD 35
Layward L 78
Lee CS 45
Lee JC 53
Lehto I 32
Lenox ES 102
Leser HG 110
Levin M 2
Levitt RC 12
Lewensohn R 72
Lieu H 79
Lin TY 45
Lindnerova G 70
Lischner HW 77
Loveless SE 114
Ludwig C 130
Ludwig R 130
Luini W 55
Lusis AJ 131
Lusis AJ 83
Lykke AW 59
Lynch M 44
Maeta M 80
Mannick JA 50
Marbache E 71
Marini M 10
Marotti T 30
Martelli MF 43
Martin F 119
Martin WJ 100
Martin WJ 54
Martin WJ 96
Masucci M 94
Mathe G 33
Mathe G 88
Matousek J 70
Matsumoto M 116
Mauritzon N 118
McCool RE 41
McMillan EM 122
Mekori T 143
Meltzer MS 112
Merino F 99
Meruelo D 100
Messner HA 131
Mickshe M 141
Mickshe M 90
Mikami N 20
Miller DR 87
Miller G 81
Milton GW 91
Mingari MC 82
Misko IS 92
Miyazaki M 21
Miyoshi I 74
M[illegible]han RA 1[illegible]1
M[illegible] TE 17
Moore T 81
Morantz RA 14
Moreau JF 73
Moretta A 82
Moretta L 82
Morgan J 121
Moroz C 142
Morton DL 133
Muchmore AV 128
Murphy MJ 137
Murphy SG 121
Murray E 91
Muta T 18
Nagino H 103
Nakamura RM 112
Nakayama S 16
Nathanson SD 102
Nayak SK 93
Neumann CG 34
Neville ME 77
Nilsson K 76
Noonan FP 63
Nordman E 32
Norman A 40
Nussbaum-Blumen 3
Nussbaum-Blumer 95
O'Leary P 85
Obrecht JP 130
Ogawa K 20
Ogiu T 65
Oh WS 46
Ohtani Y 20
Ohtsuki Y 74
Okamoto S 129
Okui K 21
Olofsson T 118
Olsson I 118
Olsson L 33
Olsson O 119
Onikul SR 50
Osaki Y 80
Oshitani T 26
Oth D 144
Ozer H 3
Ozer H 95
Pandolfi F 36
Pankina VKh 25
Paolucci P 78
Park MS 133
Parker JW 139
Parmiani G 99
Pasqualini RS 44
Pattengale PK 76
Penny R 59
Perlin E 29
Perrella FW 85
Pessano S 13
Peyrat MA 73
Pierrez J 71
Pilch YH 93
Pileri A 31
Pledger JV 22
Pope JH 92
Pross HF 135
Pujato D 44
Pykhtina AA 106
Quentmeier A 6
Quesada J 121
Rambotti P 43
Rapson NT 78
Ratliff TL 41
Ray PK 62
Raychaudhuri S 62
Reid JW 29
Reizenstein P 115
Resch K 110
Rezzonico R 2
Richens ER 22
Ringborg U 72
Robert F 144
Robinson E 143
Robinson J 81
Rogers MJ 98
Rola-Pleszczyns 79
Rollins-Smith L 66
Rosenfeld C 28
Rosenfeld C 5
Roush GC 9
Rubin P 135
Rup BJ 69
Rybkin MP 19
Rytwinski K 47
Saiga T 1
Saito O 145

Saito O 65
Saitoh A 15
Sakakibara N 20
Salem P 75
Sallstrom J 76
Salmanova EA 19
Samak R 48
Sandru G 84
Sardi J 44
Sato T 24
Saunders GC 138
Savage RA 4
Saviotti F 10
Saxton RE 133
Schirrmacher V 98
Schirrmacher V 99
Schmidt W 64
Schmitt-Verhuls 108
Schneiberg K 47
Schooneman F 71
Schulof RS 87
Schulz M 38
Schwartz DH 97
Scott JW 98
Segal R 143
Segal S 105
Seiji K 102
Sendo F 102
Senn HJ 89
Serrou B 28
Serrou B 5
Serrou B 88
Sharma JM 67
Sheedy D 95
Shibusawa M 56
Shibusawa M 57
Shimizu N 80
Shiraishi Y 74
Sihvola M 127
Simonsson B 76
Slease RB 36
Slowiaczek P 124
Smiley R 109
Soehnlen BJ 17
Soldateschi D 55
Song SK 46
Soothill JF 78
Soucek J 70
Soulillou JP 73
Spits H 126
Stanley P 17
Stass SA 8
Steinherz P 87
Steinkamp JA 138
Stewart CC 138
Stewart D 121
Strong DM 36
Stuart RK 12
Sundstrom C 76
Sutiagin AG 25
Suzuki M 24
Swain SL 96
Tagliabue A 55
Taguchi H 74
Tajima K 11
Takagi K 116
Takahashi T 16
Taki T 116
Tanaka T 145
Taniguchi M 129
Tattersall MH 124
Taylor CR 139
Teodorescu A 37
Teodorescu M 37
Terasaki PI 133
Terhorst C 126
Testa U 75
Tetaud C 75
Thomson DM 102
Toivanen A 32
Tokuhisa T 129
Tomida M 49
Tominaga S 11
Tomioka H 129
Toohey JI 120
Troxler M 130
Truitt RL 102
Tsuchida S 15
Tuma GA 7
Tung TC 45
Tura S 10
Tursz T 75
Uchida A 141
Uchida A 90
Ungerleider JS 137
Usui T 145
Vainchenker W 75
Valenzuela R 4
Vanky F 94
Vardiman J 27
Velardi A 43
Veraguth P 84
Vie H 73
Vose BM 68
Wada T 24
Wainberg MA 107
Wakabayashi S 129
Wang BS 50
Warren L 13
Wasik R 122
Watabe S 102
Weber B 71
Weisbart RH 83
Wellhausen SR 114
Weyand C 123
Wigzell H 76
Wilson JS 138
Wing MA 132
Wing MA 7
Wood GW 14
Wright J 81
Yagawa H 20
Yamada Y 18
Yamamoto Y 49
Yamashita T 51
Yamaya T 15
Yanes B 137
Yoshida Y 15
Yoshimoto S 74
Young TH 50
Ythier A 73
Zander A 121
Zarling JM 100
Zerfas AJ 34

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IMMUNOBIOLOGY AND CANCER

Functional Aspects of Cellular Immunity

SERIES CB15 No. 82/06

JUNE, 1982

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In this issue:

- EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS 1-47
- EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS 48-65
- EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION 66-94
- THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE 95-106
- ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY 107-108
- RELATED BIOLOGY OF IMMUNE CELLS 109-120
- SUPPRESSOR CELL ACTIVITY 121-125
- OTHER RELATED STUDIES 126-136

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. IN VITRO CYTOTOXICITY IN AN IMMUNOLOGIC STUDY OF HUMAN GLIOBLASTOMA.

Parente R, Bucci Sabattini MA, Servadei F
Laboratorio Analisi, Ospedale M. Malpighi, Bologna, Italy
Boll Soc Ital Biol Sper; 57(15):1635-1641 1981

In vitro cytotoxicity (CT) was studied with the aid of cultured tumor cells from histologic specimens of human glioblastomas (GB). The study included 19 patients (30-59 yr old, av

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age 48 yr, 13 females and 3 males) with GB of Grade III and IV before the start of chemotherapy, 11 healthy control s (HC; 20-35 yr old), and 9 patients with bladder carcinomas (BC). The cells were cultured according to previously published technique and used after one or two transfers. Boyum technique was used for preparation of lymphocytes from fresh, peripheral venous blood. One CT test was mediated by lymphocytes of chronic myelocytic leukemia (CML) according to Cerottini and Engers, and the other was antibody-dependent cell CT (ADCC). Using CML test with lymphocytes from patients with GB, the increase in CT for each group on the av was as follows: GB (37.09 +-3.67%), HC (4.00 +-1.78%), and BC (2.27 +-0.90%). Using CML test with lymphocytes from HC, the following results were obtained: GB (4.90 +-1.51%), HC (2.13 +-0.97%), an BC (1.13 +-0.45%). Using ADCC test with lymphocytes from patients with GB the results were as follows: GB (20.57 +-9.77%), HC (29.18 +-6.67%), and BC (27.66 +-8.51%). CML test indicates activity of NK cells, while ADCC reflects activity of K cells. The difference in results could depend also on inhibitory factors present in serum. (12 Refs) (In ITA)

2. STUDIES OF T AND B LYMPHOCYTES IN GYNECOLOGICAL MALIGNANCIES.

Sun Y, Li C, Zhang G, Kuang Y
Women's Hosp., Shanghai First Medical Coll., Shanghai, People's Republic of China
Zhonghua Fuchanke Zazhi; 16(2):93-96 1981

Lowered cellular immunity is often observed in cancer patients, which was related to their clinical conditions and prognosis. Immunological findings are described for 22 cases (34-74 yr old) of gynecologic malignancies, consisting of 12 cases of cervix carcinoma, 5 of uterine carcinoma, 3 of ovarian carcinoma, 1 of uterine sarcoma and 1 of choriocarcinoma. The majority of patients have not undergone treatment. Based on immunological examination of peripheral B- and T-lymphocytes and skin tests using old tuberculin, streptokinase-streptodornase and phytohemagglutinins, the cellular immunity in malignant gynecologic tumors was inhibited, with positive skin reaction, total T-lymphocyte count and active E-rosette formation markedly lower than those of controls. The percentage of lymphocytes and the absolute values of E-rosettes were related to the pathological stage of the tumor. The value of using E-rosettes in the immunologic evaluation of lymphocytes is discussed. (8 Refs) (In CHI)

3. ACID NONSPECIFIC ESTERASE ACTIVITY IN HUMAN LYMPHOCYTES.

Liao Y, Pan J, Li J
Dept. of CLinical Res., Chinese PLA Wuhan Army General Hosp., Wuham, People's Republic of China
Zhonghua Neike Zazhi; 20(6):352-354 1981

Acid nonspecific esterase activity was studied in human peripheral blood lymphocytes, phytohemagglutinin (PHA)-stimulated T-lymphocytes, E-rosette cells and guinea pig mononuclear macrophages. peripheral blood lymphocytes were obtained from 50 blood donors; PHA-stimulated T-cells and E-rosette cells were obtained from 10 each of patients with various types of cancers and other diseases. Positive enzyme reaction observed was 63.5 +-6.16%, in the blood donor group, 81.7% in the activated T-cell group, 80.3% in the E-rosette group and 93.2% in guinea pig macrophages. In the first group, the enzyme positive rates increased with increasing time of cell culture. Thus, the positive rate was 66.1% after 3 hr of incubation as opposed to 82.3% after 6 hr of incubation. (5 Refs) (In CHI)

4. GAMMA (IMMUNE) INTERFERON PRODUCTION BY LEUKOCYTES FROM A PATIENT WITH A TG CELL PROLIFERATIVE DISEASE.

Hooks JJ, Haynes BF, Detrick-Hooks B, Diehl LF, Gerrard TL, Fauci AS

NIDR, NIH, Building 10, Room 2B19, Bethesda, MD, 20205

Blood; 59(1):198-201 1982

We report a patient with a disease characterized by proliferation of T cells with Fc receptors for IgG (TG). However, unlike lymphoid cells from normal individuals or from patients with other lymphoid malignancies, the patient's lymphocytes spontaneously produced gamma interferon (IFN-gamma) in vitro. The peripheral lymphocytes consisted of 95% TG cells, which exhibited the morphological characteristics of T-cell chronic lymphocytic leukemia (CLL) and were normal on cytochemical and chromosome analysis. The majority of TG cells were OKT3+, OKT8+, and OKT4-, 3A1-. These cells failed to express suppressor cell activity and displayed depressed levels of natural killer activity, but mediated antibody-dependent cell-mediated cytotoxicity. The spontaneous production of IFN-gamma by human peripheral lymphoid cells as demonstrated in this study may serve as a probe for studying the relationship between IFN-gamma and the proliferation of human T-cell subsets. (Author abstract) (16 Refs)

5. THE IMMUNOBIOLOGIC PROBLEM OF SENESCENCE.

Montella F, Voci MC, Aiuti F

Istituto di III Clinica Medica Generale, Universita di Roma, Roma, Italy

Recenti Prog Med; 71(2):185-201 1981

Immunobiologic problems of senescence (Se) are reviewed with respect to biological theories, immunologic changes (morphologic changes in thymus and other lymphatic organs, changes in stem cells, in macrophages and monocytes, in T and B lymphocytes, and in K and NK cells), clinico-immunologic changes (infectious, neoplastic, and autoimmune diseases), and the possibility of therapeutic control of immunosuppression (by diet, genes, and substances that change or stimulate immunity). (161 Refs) (In ITA)

6. ANTILEUKEMIC CELLULAR IMMUNITY IN CHILDREN WITH ACUTE LYMPHOID LEUKEMIA UNDERGOING IMMUNOTHERAPY.

Bergolits VM, Osipov SG, Eremeev VS, Rumiantsev AG, Akimova GV

Lab. Experimental Tumor Therapy, P. A. Hertsen Oncological Inst., Moscow, USSR

Probl Gematol Pereliv Krovi; 26(11):12-14 1981

Effect of immunotherapy on cellular immunity was studied in 30 children with acu te lymphoblastic leukemia (ALL). Induction therapy consisted of vincristine and prednisolone alone or in combination with administration of autologous blocking antibodies IgG and IgM. During remission, the patients received maintenance chemotherapy alone or in combination with BCG vaccine. Administration of IgG and IgM inhibited synthesis of antibodies blocking the antileukemic effect of immune lymphocytes. Maintenance therapy with BCG vaccine resulted in significant stimulation of cytotoxic killer cells. (9 Refs) (In RUS)

7. T CELL LEUKEMIA PRESENTING AS CHRONIC POLYARTHRITIS.

Van Soesbergen RM, Feltkamp-Vroom TM, Feltkamp CA, Somers R, Van Beek WP
Dept. Rheumatology, Slotervaart Hosp., Louwesweg 6, 1066 EC, Amsterdam, The Netherlands
Arthritis Rheum; 25(1):87-91 1982

The case of a 30-yr-old woman with T cell chronic lymphocytic leukemia presenting as seronegative chronic polyarthritis is described. No liver or spleen enlargement was found initially. Ninety to 95% of the peripheral blood lymphocytes were positive with anti-T cell serum and formed E rosettes. T cell infiltration was found in bone marrow, synovial fluid, and nodules resembling rheumatoid skin lesions. Therapy with chlorambucil relieved the symptoms temporarily; the patient eventually died after a short illness. Differentiation between chronic polyarthritis and lymphocytic leukemia can be difficult due to similar presenting symptoms. (26 Refs)

8. CORRELATION OF CIRCULATING IMMUNE COMPLEXES AND DISEASE STATUS IN PATIENTS WITH LEUKAEMIA.

Hubbard RA, Aggio MC, Lozzio BB, Wust CJ
(c/o Wust) Dept. Microbiology, Univ. Tennessee, Knoxville, TN, 37916
Clin Exp Immunol; 43(1):46-53 1981

The occurrence of soluble immune complexes (IC) was investigated in 177 serum samples from 92 patients with various leukemias using the Raji cell immunoassay. In general, patients with myeloproliferative diseases had a higher incidence and higher quantities of IC than did patients with lymphoproliferative disorders. Elevated levels of IC were found in the sera of patients as follows: 17% with chronic lymphocytic leukemia (mean value of 13.1 ug/ml), 67% with acute lymphocytic leukemia (54.1 ug/ml), 65% with chronic myelocytic leukemia (86.7 ug/ml), 70% with acute myelocytic leukemia (202.5 ug/ml) and 56% with acute myelomonocytic leukemia (41.9 ug/ml). Patients in terminal blastic crisis of chronic myelocytic leukemia had the highest levels, with a mean level of 1,364.1 ug/ml. Serial samples were obtained, as available, from individual patients during the course of the disease in an attempt to relate severity with the incidence and quantity of IC. No significant correlation could be made between the occurrence or levels of IC and the presence or absence of systemic symptoms. Similarly, no correlations could be made between levels of IC and hema tological parameters, infection, or therapy. However, the data does indicate a positive relationship between the levels of IC and the progressive state of the leukemia, especially, the myelocytic leukemias. (Author abstract) (27 Refs)

9. FUNCTIONAL STUDIES ON B CELLS IN HUMAN BONE MARROW: IN VITRO MITOGEN STIMULATION OF NORMAL AND MALIGNANT B CELLS.

Hammarstrom L, Smith CI, Pettersson D, Mellstedt H, Holm G
Dept. Immunobiology, Wallenberg-laboratory, Karolinska Inst., Lilla Frescati, S-104 05 Stockholm 50, Sweden
Clin Exp Immunol; 43(1):157-164 1981

Using the protein A plaque assay, bone marrow cells from normal donors were shown to secrete spontaneously immunoglobulins mainly of the IgG and IgA class. After mitogenic activation, a marked increase in IgM production was observed with kinetics and cell density requirements similar to that of blood lymphocytes. In Morbus Waldenstrom patients, IgM was the predominant Ig class secreted spontaneously by bone marrow cells. The high in vitro background proliferation of these cells could be abolished by addition of the appropriate anti-idiotypic antiserum. After stimulation with mitogens, differentiation of cells within the malignant clone to immunoglobulin-secreting lymphocytes was evidenced, suggesting a retained responsive capacity of the transformed cells. (Author abstract) (27 Refs)

10. MONOCYTE FUNCTION IN HODGKIN'S DISEASE.

Holm G, Bjorkholm M, Johansson B, Mellstedt H, Lindemalm C
Institutionen for klinisk immunologi, Huddinge sjukhus, 141 86 Huddinge, Sweden
Clin Exp Immunol; 47(1):162-168 1982

Monocyte functions were studied in 16 patients with Hodgkin's disease, 11 untreated and 5 in unmaintained complete remission. Eleven untreated patients with non-Hodgkin's lymphomas and 21 healthy persons were used as controls. Monocytes were isolated from peripheral blood and enriched to greater than 90%. Lymphoma monocytes showed normal ability to lyse human RBC coated with anti-D IgG antibodies as evaluated by a 51Cr-release assay. The ability of monocytes to augment or suppress concanavalin A stimulation of lymphocytes purified to greater than 98% was studied by incubation of a number of lymphocytes with increasing amounts of purified monocytes. The incorporation of 14C-thymidine was potentiated by a factor of 10 in the presence of equal amounts of monocytes. There was no difference between monocytes from Hodgkin, non-Hodgkin or healthy controls to augment patients' autologous or normal lymphocytes. Patient monocytes also suppressed the response at the same monocyte-lymphocyte ratio as normal monocytes. Stimulation of patient lymphocytes without the addition of monocytes was usually lower than that of normal control lymphocytes. The difference between patient and control lymphocyte stimulation was preserved in the presence of monocytes. It is concluded that monocytes from patients with active Hodgkin's disease or non-Hodgkin's lymphoma have normal helper and suppressor effects on patient or normal lymphocytes stimulated by Con A and normal antibody-dependent cytotoxicity. (Author abstract) (31 Refs)

11. SHORT-TERM EFFECT OF IRRADIATION ON THE PERIPHERAL LYMPHOCYTE POPULATIONS IN PATIENTS TREATED WITH HIGH-ENERGY PHOTON BEAM.

Fekete B, Petranyi J, Reischl G, Gyarmathy I
Natl. Inst. Tuberculosis and Pulmonology, P. O. Box 1, H-1529 Budapest, Hungary
Strahlentherapie; 157(8):542-543 1981

Changes in lymphocyte populations were studied in 22 patients with testicular cancer before and after a single 2-Gy dose of high-energy photon beam. Absolute lymphocyte counts as well as total T-and active T cells markedly decreased immediately after irradiation, whereas no significant alterations in Fc receptor-bearing lymphocytes and B cell counts were produced. Recovery of lymphocyte populations was relatively rapid, reaching pre-irradiation values by 24 hours. (Author abstract) (14 Refs)

12. LYMPHOCYTOTOXIC ANTIBODIES IN CANCER.

Schocket AL, Malesk, CV, Kohler PF
Div. Clinical Immunology, Dept. Medicine, Univ. Colorado Health Sciences Center, 4200 East Ninth Ave., Denver, CO, 80262
Cancer Immunol Immunother; 12(1):43-47 1981

Cold-reactive lymphocytotoxic antibodies (LCA) were measured in sera from 71 patients with various malignancies and 31 healthy controls. Cytotoxicity indices were elevated much more frequently in the sera from lymphoreticular malignancy (LM) patients (10/24) than in the sera from chronic lymphocytic leukemia (0/9), melanoma (5/22), carcinoma (1/16) of the breast, bowel, lung, or uterus patients, or those from normal controls (1/31). In the LM group LCA levels were not correlated with delayed hypersensitivity skin tests, skin croton oil response, total lymphocytes, T cells, or B cells. While LCA is apparently increased in patients with LM, the response is evidently not related to defects in the cell-mediated immune system in some of the patients. (36 Refs)

13. SPONTANEOUS CELL-MEDIATED CYTOTOXICITY IN PATIENTS WITH TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER. DIFFERENCE IN EFFECTOR CELL POPULATION.

Moroz C, Lindner A, Twig S, Madgar I, Many M
Rogoff-Wellcome Medical Res. Inst., Beilinson Medical Center, Petah-Tikva, Israel
Cancer Immunol Immunother; 12(1):57-62 1981

Spontaneous lymphocyte-mediated cytotoxicity (SLMC) of peripheral blood lymphocytes (PBL) from patients (male, av age 71) with transitional cell carcinoma (TCC) of the urinary bladder was studied. SLMC of PBL against K-562 cells varied greatly, but PBL from controls and patients did not differ in cytoxic activity over a range of effector:target ratios. Following separation of effector cells i nto T and non-T fractions, SLMC of T lymphocytes derived from TCC patients was significantly greater than that of non-T cell populations. In controls, cytotoxic activity of non-T cells was higher than that of T cells. Repeated experiments on two TCC patients over a 1 yr period consistently showed the high SLMC of T lymphocytes. The relatively higher SLMC of T cells from TCC patients was even more profoundly exhibited when Peer cells instead of K-562 cells were targets. Neither treatment with monoclonal antibodies OKT 8 or OKT 4 and complement nor use of preparations depleted of Fc-receptor-positive cells could abolish the cytotoxicity of T cells from cancer patients. The natural killer-like T cells are thought to be a disease-related phenomenon, but their nature remains unclear. (35 Refs)

14. INFLUENCE OF ORAL BM 12531 (INN AZIMEXON) ON IMMUNE RESPONSE IN UNTREATED CANCER PATIENTS. A RANDOMIZED DOUBLE-BLIND STUDY.

Heim ME, Massner B, Knebel L, Stosiek U, Boerner D, Bicker U
Onkologisches Zentrum, Universitat Heidelberg, 6800 Mannheim 1, W. Germany
Cancer Immunol Immunother; 12(1):87-90 1981

A randomized double-blind trail of the effects of azimexon (3 x 100 mg/day po for 7 days) on immune function was performed in 30 unselected patients with different solid tumors. No effect of azimexon could be shown on total or active T-lymphocyte counts or on 3H-thymidine uptake in the lymphocyte blastogenesis response, with or without mitogens. Red blood cell count and hemoglobin concentration showed a significant decrease in the treated subjects; reticulocytes simultaneously increased. Some slight but insignificant changes in immunoglobulins were observed. The major side effect was a decline of 4 g hemoglobin/100 ml in patients receiving 900 mg azimexon daily; dosage greater than 300 mg daily should be avoided. (12 Refs)

15. COMPARISON OF SERUM BLOCKING FACTORS ON LEUKOCYTE ADHERENCE INHIBITION AND PHA LYMPHOCYTE BLASTOGENESIS IN BREAST CANCER PATIENTS.

Fujisawa T, Yonemoto RH, Waldman SR
Dept. Surgery, Inst. Pulmonary Cancer Res., Chiba Univ. Sch. Medicine, 1-8-1, Inohana, Chiba 280, Japan
Jpn J Surg; 11(6):406-412 1981

Correlation between specific and nonspecific blocking factors, and tumor burden in patients with breast cancer (BC) were studied. Modified leukocyte adherence inhibition (LAI) assay and phytohemagglutinin-induced blastogenesis assay were used in the study. Serum blocking factors (SBF) in sera from 48 patients with BC were examined. Specific SBF in LAI assay were detected in 15/21 patients with recurrence, in 5/11 with local or regional involvement, and in 3/16 with no evidence of the disease (NED). Significant differences were found between patients with recurrence of the disease and patients with NED. SBF in LAI and lymphocyte blastogenesis (LB) correlated in 29/48 patients; 9/48 SBF positive in LAI and LB , 20/48 SBF negative in LAI and LB. SBF in LAI was demonstrated in 14/48 patients whose sera showed no SBF in LB. Results indicate that SBF in LAI and LB are either induced or derived from BC tissue. SBF in LAI correlates closely with the tumor burden. SBF in LB shows less correlation. LAI assay shows good potential use as routine clinical test for detection of cell-mediated immunity. SBF, directed to tumor-associated antigens, shows potential use for evaluation of immunocompetence, residual tumor burden, and as a guide to therapeutic effects in cancer patients. (21 Refs)

16. THE CYTOLYTIC ACTIVITY OF T LYMPHOCYTES PRESENT WITHIN TUMOUR TISSUE OBTAINED FROM PATIENTS WITH MELANOMA (MEETING ABSTRACT).

Burns GF, Riglar C, Mackay IR
No affiliation given
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Cultures of T lymphocytes were established from 6 to 7 samples of tumor tissue freshly resected from patients with melanoma. The lymphocytes were grown in culture medium containing a source of T cell growth factor (TCGF, IL2) and morphological, cytochemical and immunological studies with a panel of monoclonal antibodies confirmed that the cultures were of pure T cells. Great care was taken to ensure that the cultured T cells did not originate from blood contaminating tumor tissue and, initially at least, the cytolytic activity of the cultured cells differed from that of T cells grown from peripheral blood in TCGF. The T cells grown from two patients were expanded in culture and tested for cytolytic activity against (a) autologous tumor cells frozen directly from the tumor cell suspensions, (b) autologous and allogeneic melanoma cells from primary cultures of tumor, (c) autologous and allogeneic EBV-transformed B lymphoblasts, (d) melanoma cell lines and (e) a Chang cell line. Initially T cells derived from both tumor tissues showed high cytolytic activity against fresh autologous and allogeneic melanoma cells but less against the melanoma cell lines and little or no activity against B lymphoblasts. After 2 wk culture, however, the T cells grown from the tumor showed similar cytolytic activity to normal peripheral blood cells grown in TCGF in being highly active against a range of target cells with no demonstrable specificity. (no Refs)

17. IMMUNOGLOBULIN E IN CHILDREN WITH LEUKEMIA AND MALIGNANT LYMPHOMA.

Chmielewska D, Gutkowska J, Matysiak M

Klinika Hematologii i Pneumologii, IP AM, ul. Dzialdowska 1, 01-184 Warsaw, Poland

Pediatr Pol; 56(9):1059-1064 1981

The serum IgE levels were determined in 120 children (3 mo to 16 yr old) with acute lymphoblastic lymphoma (104 patients), Hodgkin's disease (8) and non-Hodgkin's lymphoma (8). Elevated IgE levels were found in 6/104 patients with leukemia. This incidence (5.7%) is not higher than that which may occur in the general population. The IgE levels were also elevated in 1/8 patients with non-Hodgkin's lymphoma and in 2/8 with Hodgkin's disease. E rosette tests were performed in vitro once or several times in 34 of the patients. The results of the E rosette tests were disturbed in over half the tested patients with leukemia. The values of the rosette tests were below 30% in nearly one third of the patients. Lymphocyte stimulation tests with thymus factor X were performed in 36 patients. Stimulation led to a rise in the percentage of rosette-forming lymphocytes in 29/36 patients. No correlation was found between the IgE levels and reduced value of the rosette test. (27 Refs) (In POL)

18. TRIALS OF IMMUNOSTIMULATION WITH LEVAMISOLE IN CHILDREN WITH MALIGNANT NEOPLASMS.

Newecka-Samol T, Ochocka M

Klinika Hematologii i Pneumologii, IP AM, ul. Dzialdowska 1, 01-184 Warsaw, Poland

Pediatr Pol; 56(9):1065-1070 1981

Trials of immunostimulation with levamisole (2 mg/kg/day po on 2 consecutive days of the wk, for 12 wk) were carried out in 14 children with acute lymphoblastic leukemia (ALL), 5 adults with Hodgkin's disease (HD), 1 with non-Hodgkin lymphoma, one child with hemolytic anemia and another with Wissler-Fanconi syndrome. Frequent respiratory infections of considerable severity were the indications of levamisole treatment. Six children with ALL (Group 1) were treated during remission without treatment, nine others (Group 2: eight patients with ALL and one with NHL) were treated during chemotherapy. Four out of five patients in Group 3 were in remission without treatment, the fifth was treated with levamisole during chemotherapy. The E rosette tests and determinations of the leukocyte, granulocyte and lymphocyte counts before and after levamisole treatment showed that patients with impaired cell-mediated immunity and reduced initial E rosette test values benefitted most from the levamisole therapy. Levamisole treatment was found to stimulate the granulocytes, but its effect on other laboratory parameters was less evident. The levamisole treatment reduced the frequency of infections and alleviated their course considerably. No side-effects were observed. The findings indicate that levamisole can be used as a supplement of cytostatic therapy in patients with neoplasms. (23 Refs) (In POL)

19. SEM OBSERVATION OF CULTURED, MITOGEN-STIMULATED LEUKOCYTES, CELLS OBTAINED FROM PATIENTS WITH ACUTE MYELOBLASTIC AND CHRONIC LYMPHOCYTIC LEUKEMIAS.

Lalague ED, Abugaber AA, Haviernick S, Corvellec MR, Pelletier L, Derghazarian C, Cousineau GH

Laboratoire de Biologie Moleculaire, Departement de Biologie, Universite de Montreal, C. P. 6128, Montreal, Quebec, H3C 3J7, Canada

Experientia; 38(1):90-92 1982

SEM observation of acute myeloblastic leukemia cells, incubated for 20 hr with the mitogens pokeweed and phytohemagglutinin, showed these to have elongated structures that were either smooth or partially covered by thumblike figures. By contrast, the chronic lymphocytic leukemia cells possessed more compact shapes and some were covered with blebs of varying sizes. (Author abstract) (10 Refs)

20. ALLOREACTIVE CYTOTOXICITY OF INTERFERON-TRIGGERED HUMAN LYMPHOCYTES DETECTED WITH TUMOR BIOPSY TARGETS.

Vanky F, Klein E

Dept. Tumor Biology, Karolinska Institutet, S-10401 Stockholm 60, Sweden

Immunogenetics; 15(1):31-39 1982

Interferon activation of lymphocytes produces lytic potential against allogeneic but not against autologous biopsy-derived tumor cells. This effect was seen when targets isolated from solid tumors were used directly without cultivation in vitro. The hypothesis that the lytic effect was due to activation of alloreactive cells was tested in the cold target competition assay. The results substantiated our assumption because they showed that in a given lymphocyte population separate sets act on allogenic tumor cells derived from different individuals. In addition PHA blasts from the target-cell donor but not from unrelated individuals also inhibited the lysis. The system we use is operationally an NK assay in which antigen (MHC)-recognizing lymphocytes seem to function. Since antigen recognition is a property of the T subset, the conceptual dualism in the classification of NK and CTL effects should be modified. (Author abstract) (25 Refs)

21. INFLUENCE OF SPLENECTOMY UPON IMMUNOLOGIC REACTIVITY OF PATIENTS WITH HODGKIN'S DISEASE.

Rogan-Grgas J, Milas L, Hauptmann E, Nola P, Kolaric K, Maricic Z, Malenica B

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Tumori; 67(6):539-547 1981

Since most patients with Hodgkin's disease benefit from splenectomy, a study was designed to explore whether these beneficial effects could be attributed to the recovery of patients' immunologic reactivity. Using a series of ordinary skin test (PPD-tuberculine, Varidase and Candidin) determination of absolute T and B lymphocyte counts in peripheral blood and their mitogenic responsiveness, assessment of immunologic reactivity was performed in 28 Hodgkin's disease patients, prior to and 14 days after splenectomy. The results showed that overall immunologic reactivity of these patients was suppressed as judged by low absolute lymphocyte counts (1,747.2 +-171.9), lower counts of T (592.0 +-92.1) and B cells (295.9 +-40.5) and their poor capacity to respond to phytohemagglutinin (PHA) (20,342.6 +-3,662.8 cmp), although the reactivity towards skin test antigens seemed to be well preserved. After splenectomy the reactivity improved, absolute lymphocyte counts raised to 2,654.9 +-468.8 and were parallelled by an increase in T (936.7 +-138.0) and B cell counts (402.2 +-81.2). PHA reactivity recovered as well (26,965.5 +-4,035.6 cpm), however, its remained lower than in control cultures. Furthermore, the immunocompetence of patients' spleens was assessed. The possible influence of some suppressive mechanisms such as serum-blocking factor and prostaglandins is discussed. (Author abstract) (45 Refs)

22. STUDY OF CERTAIN PARAMETERS OF IMMUNE REACTIVITY IN CHILDREN WITH NEUROBLASTOMA.

Siwinska-Golebiowska H, Kunicka A, Borysewicz G, Nowakowska K, Smogorzewska E, Duros H, Perek D, Bozek J

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Pediatr Pol; 56(8):889-896 1981

Certain parameters of cell-mediated and humoral immunity were determined repeatedly before and during treatment in 24 children with neuroblastoma. The reactivity of peripheral blood lymphocytes, the T and B cell counts, the spontaneous reduction of nitroblue tetrazolium, and the IgG, IgA, IgM, and IgD levels were determined. Before treatment, the humoral immunity was within normal limits or raised in most children, while the cell-mediated immunity, especially the lymphocyte reactivity, was somewhat decreased. Decreases in the parameters of cell-mediated immunity (especially in lymphocyte reactivity) were observed during treatment. The immunosuppressive effect of x-ray therapy was found to be much stronger than that of chemotherapy. The IgG, IgA and IgM levels decreased to normal values or to below twice the standard deviation during treatment. The decrease was most pronounced in the IgM levels. (20 Refs) (In POL)

23. BLOOD LYMPHOCYTE SUBPOPULATIONS IN MYCOSIS FUNGOIDES AND THEIR FUNCTIONS IN VITRO.

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Acta Derm Venereol (Stockh); 61(6):487-490 1981

T-lymphocyte subpopulations, PWM stimulated in vitro Ig production by mononuclear cells, and spontaneous cell-mediated cytotoxicity (SCMC) were determined in patients with Mycosis fungoides (MF) as well as in sex- and age-matched normal controls. We were able to confirm our earlier findings of a significantly higher frequency of T-lymphocytes with Fc-receptors for IgG (Tg cells) and a proportion of T lymphocytes with Fe receptors for IgM (Tm cells) not significantly differing from normal controls. As defined by monoclonal antibodies, the proportion of T-helper cells (Leu3A) was significantly lower, whereas the T-suppressor cells (Leu2A) were in the range of normal controls. The PWM stimulated and spontaneous Ig synthesis in vitro was lower in MF patients whereas there was no difference in the SCMC activity, in comparison with normal controls. The lower frequency of T-helper cells in the peripheral blood may be e xplained by their migration to the skin. (Author abstract) (14 Refs)

24. LYMPHOMATOID PAPULOSIS: A CUTANEOUS T-CELL PSEUDOLYMPHOMA.

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Acta Derm Venereol (Stockh); 61(6):491-496 1981

It was the purpose of this study to further define the nature of the dermal infiltrates in lymphomatoid papulosis (LP) by means of enzyme cytochemistry (acid phosphatase and esterase), immunology (rosetting techniques, immunoperoxidase technique on cryostat sections), and by semithin and ultrathin sections. The studies performed on biopsy samples with clinically and histologically typical LP indicated that most lymphoid cells display markers for T-lymphocytes, which were helper T-cells in the one case studied with monoclonal antibodies. Regarding the typical benign self-involutive clinical course, LT is considered to be a cutaneous pseudolymphoma of T-cell type. (Author abstract) (24 Refs)

25. T LYMPHOCYTES WITH FC-IGG RECEPTORS IN SKIN CANCERS.

Vena GA, Angelini G, D'Ovidio R, Lospalluti M, Meneghini CL

Dept. Dermatology, Univ. Bari, Bari, Italy

Acta Derm Venereol (Stockh); 61(6):555-558 1981

The proportion of peripheral blood lymphocytes with receptors for the Fc fragment of IgG (Tg) has been investigated in 25 patients with squamous cell carcinoma of the skin, in 25 patients with basal cell carcinoma of the skin, and in 33 controls. In patients with squamous cell carcinoma the results showed elevated values for Tg lymphocytes and a negative correlation between these T cells and the lymphocyte response to PHA and ConA. In patients with basal cell carcinoma the values for Tg lymphocytes were normal. (Author abstract) (12 Refs)

26. MONOCLONAL BLOOD LYMPHOCYTES IN BENIGN MONOCLONAL GAMMOPATHY AND MULTIPLE MYELOMA IN RELATION TO CLINICAL STAGE.

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Scand J Haematol; 27(4):287-293 1981

Twenty patients with benign monoclonal gammopathy (BMG) have been studied for blood lymphocyte and subpopulations. Four patients had slightly decreased T-lymphocyte values. Total B-lymphocytes were within the normal range. In three BMG patients an abnormal ratio between chi- and lambda-bearing lymphocytes was detected indicating circulating monoclonal cells. Forty-one patients with untreated multiple myeloma have also been analyzed for blood monoclonal lymphoid cells using the chi:lambda-ratio. Fifty-four percent of the patients had monoclonal blood cells at diagnosis. The incidence and numbers of such cells increased with advanced clinical stage. Thus, it seems as if tumor volume is the main factor responsible for the appearance of monoclonal blood cells in multiple myeloma. (Author abstract) (23 Refs)

27. THE LYMPHOCYTE-EPITHELIAL CELL RATIO IN TUBAL MUCOSA OF PATIENTS WITH CERVICAL CARCINOMA.

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Pathol Res Pract; 173(1/2):82-87 1981

The lymphocytes in the luminal subepithelial basement membrane of the uterine tube from patients with cervical carcinoma were counted, and the results compared with those obtained from women of the same age but without cervical carcinoma to determine whether a relationship exists between the emigration of lymphocytes into the tubal epithelium and the clinical diagnosis of cervical carcinoma. The comparison indicated that the number of lymphocytes migrating into the tubal epithelium during the secretory and the proliferative phase in women with cervical carcinoma is significantly lower than that in healthy women from the control group. The differences during the secretory phase were particularly pronounced. The lymphocyte count in patients with cervical carcinoma was only one third that of the healthy women in the control group. Assuming that an immunologic defect is determinative for the development of carcinoma, a decline in the number of lymphocytes migrating into the tubal epithelium can be interpreted as the reflection of an immunologic deficiency. It is possible that a disturbance in the lymphocyte: epithelial cell ratio in this stage of life could indicate a disposition for those tumors the incidence of which is high in this age group (eg, squamous cell carcinoma of the cervix). Further study is necessary to establish whether these cells be classified as B or T lymphocytes. (Author abstract) (16 Refs)

28. EFFECT OF BM 12531 ON ROSETTE FORMATION AND IN VITRO FUNCTIONS OF PERIPHERAL BLOOD LYMPHOCYTES OBTAINED FROM HEALTHY DONORS AND CANCER PATIENTS.

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Indian J Med Res; 74:705-714 1981

BM 12531 a 2-cynanaziridine derivative was tested for in vitro immunomodulation of peripheral blood lymphocytes from normal healthy donors, chronic myeloid leukemia patients in remission and untreated patients with Hodgkin's disease and multiple myeloma. The in vitro functions tested were active and total E rosette formation, PHA induced blastogenesis and production of PHA induced leukocyte migration inhibition factor. It was observed that incubation of lymphocytes with the drug at three concentrations (1.5 and 12.5 ug/ml) did not affect total or active E rosette formation significantly, while lymphocytes from 8/22 (36%) subjects showed increased uptake of 3H TdR in response to PHA in combination with the drug. There was no obvious dose dependency within the drug concentrations tested, although 5 ug/ml of the drug showed more potentiating activity. The drug was most active in induction of LMI factor by mitogen, especially in experiments where, initially the mitogen alone did not produce the lymphokine. BM 12531 did not seem to potentiate effectively, the T cell functions in malignancies characterized by general immunosuppression, such as Hodgkin's disease and multiple myeloma. (Author abstract) (21 Refs)

29. THE EFFECT OF URAEMIC SERUM AND PLASMA ON PROLIFERATING CELLS IN VITRO.

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Acta Pathol Microbiol Scand [C]; 89(6):353-358 1981

Phytohemagglutinin (PHA)-stimulated lymphocytes from healthy individuals and a malignant cell-line (K-562 cells) were cultured in growth medium of 75% RPMI 1640 (Gibco) supplemented with 25% of uremic serum or plasma obtained after systemic heparinization. Pooled human A Rh + serum from three different donors served as controls. There was a depression of the DNA synthesis in both cell systems measured as uptake of methyl-3H-thymidine when the cells were cultured in uremic milieu. Systemic heparinization markedly increased the depressive effect of uremic plasma compared with controls. Heparin added to the growth media in concentrations much higher than those usually present in plasma after systemic heparinization had little effect on the cell proliferation. Systemic heparinization thus appears to induce production of toxic substances in plasma acting on proliferating cells. (Author abstract) (22 Refs)

30. DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF CHROMOSOME ABNORMALITIES IN MARROW AND MITOGEN RESPONSE OF LYMPHOCYTES OF ACUTE NONLYMPHOCYTIC LEUKEMIA.

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Cancer Genet Cytogenet; 5(1):1-24 1982

Chromsomes of bone marrow from 28 patients with acute nonlymphocytic leukemia (ANLL) (26 with AML, 2 with AMMoL), 19 of whom had chromosome abnormalities, were studied; 11 cases exhibited previously unreported karyotypic abnormalities. The marrows of two cases had 8-21 translocations associated with an iso-X chromosome in the female patient and with 9q13-and a missing Y in the male patient. Usually, AML patients with an 8-21 translocation have been considered to have a good prognosis; however, our cases had rather short survival times. Therefore, the prognosis of AML with an 8-21 translocation but associated with other abnormalities is still not clear. Centromere spreading (CS), which was originally reported in marrow cells of megaloblastic anemia (B12 and folic acid deficiency), was detected in leukemic cells, disappeared during remission, and reappeared on relapse. These findings suggest that CS may be a new type of abnormality in AML. In two patients with atypical hypoplastic anemia and hemolytic anemia, chromosome abnormalities were detected at the anemic stage. One case with CS was associated with atypical hypoplastic anemia and developed AML after 1 yr; the other with 48,XY,+i(1q),+3,+12 and-14 had hemolytic anemia and developed AMMoL 3 wk later. Interestingly, identical clones were detected both before and after the clinical diagnosis of leukemia. These cases strongly support the concept that some chromosome abnormalities precede the clinical manifestations of leukemia. The present study also revealed that lymphocytes in ANLL respond poorly to PHA in the presence of high numbers of blasts but do respond well to mitogens during remission. Therefore, the response of lymphocytes to PHA may serve as one criterion for determining remission. (Author abstract) (15 Refs)

31. DISORDERS OF LEUCOCYTES.

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Dept. Haematology, Univ. Liverpool, Liverpool, England
Practitioner; 226(1363):59,60,63,64,67-69 1982

The normal life cycles and functions, qualitative disorders, and quantitative disorders of neutrophils, monocytes, lymphocytes, and plasma cells are discussed, with emphasis on presenting symptoms. Diagnosis of preleukemia or benign monoclonal gammopathy is essentially retrospective; the distinction between chronic lymphocytic leukemia and diffuse well-differentiated lymphocytic lymphoma is often arbitrary. Acute lymphocytic leukemia of childhood may be a distinct entity from the adult form, which in any case carries a much better prognosis. Non-Hodgkin's lymphoma (NHL), in contrast to Hodgkin's disease (HD), is often disseminated at diagnosis and carries a poorer prognosis than HD. Waldenstrom's macroglobulinemia is a form of NHL associated with elevated IgM levels which requires about the same treatment as NHL with the possible addition of intensive plasmapheresis to reduce plasma viscosity. (6 Refs)

32. MONOCYTE CYTOTOXICITY AFTER SPLENECTOMY.

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Scand J Haematol; 27(4):271-278 1981

Antibody-dependent cell-mediated cytotoxicity (ADCC) by monocytes was determined in 45 adults approximately 4 years after splenectomy for either abdominal trauma or accidental injury during operation for benign gastroduodenal ulcer. Compared to controls, both groups of splenectomized persons showed increased numbers of monocytes and decreased monocyte ADCC. The decrease of monocyte ADCC was only significant in those splenectomized persons in whom accessory splenic tissue was not detectable by isotope scanning. Addition of the spleen-dependent peptide tuftsin to monocytes in vitro did not augment their ADCC. An increased serum concentration of immune complexes was demonstrated in 18% of the splenectomized persons, but this increase was neither related to the presence of splenic tissue nor to the monocyte cytotoxicity. Vaccination with pneumococcal polysaccharide had no effect on monocyte ADCC. It is suggested that the defective monocyte cytotoxicity observed in splenectomized persons without detectable splenic tissue might be relevant to post splenectomy infectious susceptibility. (Author abstract) (35 Refs)

33. ATAXIA TELANGIECTASIA AND ACUTE LYMPHOBLASTIC LEUKEMIA: REPORT OF A CASE.

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Tumori; 67(6):585-587 1981

We report a new case of ataxia-telangiectasia (AT) and acute lymphoblastic leukemia (ALL) and review all 21 known cases of AT and ALL. Leukemia in these patients is associated with a male predominance, age older than 10 yr at diagnosis, a white blood cell count higher than 50,000 mm3, and a fatal course. Four patients have been reported who developed T-cell leukemia, three null-cell leukemia and one B-cell leukemia. The AT-ALL patients appear to be at risk for infections related to their immunodeficient status and ALL chemotherapy. In addition, neurologic deterioration has been noted during the early phase of therapy. (Author abstract) (8 Refs)

34. EXPERIMENTAL ULCERATIVE HERPETIC KERATITIS. IV. PRELIMINARY OBSERVATIONS ON THE EFFICACY OF A HERPES SIMPLEX SUBUNIT VACCINE.

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Br J Ophthalmol; 65(10):679-682 1981

Intramuscular administration of an inactivated type 1 herpes simplex virus (HSV) subunit vaccine in rabbits stimulated humoral and cellular immune responses and produced good levels of protection against corneal challenge with line HSV-1 virus. (22 Refs)

35. THE HOST'S CELLULAR IMMUNE STATUS AND THERAPY FOR LIVER CANCER.

Nishioka M, Kan T, Kan M, Kodama T, Nawata J, Harada T, Nishimura H, Takemoto T
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Bull Yamaguchi Med Sch; 28(1/2):63-68 1981

The skin reactions to purified protein derivative (PPD), phytohemagglutinin (PHA) and polysaccharide antigens from streptococcal hemolyticus (PS-E), were depressed in the initial stage of the patients and markedly depressed in the end stage. The number of T-cells in peripheral blood decreased with progress of illness, but the number of PHA-blastoid cells and active T-cells increased sometimes in the end stage. It suggests that these factors as well as skin tests are useful parameters of evaluation of the cellular immune status of the patients with primary liver carcinoma. The host's immune status was impaired frequently either by the disease itself or by chemotherapy. In cases receiving chemotherapy in combination with the administration of OK-432, the depressed skin reaction to PS-E improved often. These findings suggest that the administration of OK-432 affect the host and that result of this skin test is useful as a parameter to determine the method and period of OK-432 administration and to judge its effectiveness. (Author abstract) (18 Refs)

36. MALABSORPTION SYNDROME, COCCIDIOSIS, COMBINED IMMUNE DEFICIENCY, AND FULMINANT LYMPHOPROLIFERATIVE DISEASE.

Hallak A, Yust I, Rataan Y, Adar U
Dept. Medicine H, Ichilov Hosp., Weitzman St., Tel Aviv 6, Israel
Arch Intern Med; 142(1):196-197 1982

Coccidia were found in a patient suffering from malabsorption syndrome. In addition, immunologic investigation showed combined humoral and cellular immunodeficiency. Treatment with metronidazole induced the disappearance of coccidia from the stool and clinical remission. Six months later, the patient was seen with acute lymphoproliferative disease and died thereafter. The possible relationship between malabsorption, immunodeficiency, coccidiosis, metronidazole, and malignancy is reviewed. (Author abstract) (19 Refs)

37. 'LENNERT'S LYMPHOMA' OF THE NOSE.

Zardawi IM, Kuruvilla A, Saha NK
Dept. Histopathology, The Leicester Royal Infirmary, Leicester, England
J Laryngol Otol; 95(12):1271-1275 1981

An 85-yr-old male patient presented with a left-sided nasal obstruction of 1 yr duration. Histology of the tumor revealed clusters of epithelioid histiocytes scattered among immature lymphoid cells (lymphoblasts). Immunological studies of the tumor revealed a polyclonal (B cell) pattern in only a small proportion of the lymphoid cells. A T-cell origin is proposed. The histiocytes showed intense positivity when stained for muramidase. Wide local excision of the tumor was performed and the patient remains well and free of symptoms five mo post-operatively. (Author abstract) (12 Refs)

38. STIMULATION BY INTERFERON OF INDUCTION OF DIFFERENTIATION OF HUMAN PROMYELOCYTIC LEUKEMIA CELLS.

Tomida M, Yamamoto Y, Hozumi M
Dept. Chemotherapy, Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-ken 362, Japan
Biochem Biophys Res Commun; 104(1):30-37 1982

The effects of purified human leukocyte interferon-alpha (IFA) and partially purified fibroblast interferon-beta (IFB) on induction of differentiation of human promyelocytic leukemia cells (HL-60) into granulocytes and macrophages were studied. HL-60 cells maintained for 6 days in conditioned medium of mouse myeloid leukemia M1 cells with phytohemagglutinin were induced to differentiate predominantly into monocytes and macrophages (M+Ms) in a concentration-dependent manner in concentrations up to 50% (vol/vol) of the conditioned medium. The interferons alone neither inhibited HL-60 cell growth nor induced differentiation, but both enhanced growth inhibition and induction of differentiation into M+Ms by suboptimal concentrations the conditioned medium of M1 cells. The interferons also increased macrophage inducing power of low concentrations of 12-O-tetradecanoylphorbol-13-acetate and the granulocyte inducing effect of retinoic acid. The mechanism of IFA and IFB action is not known, but it seems to differ from that of cerebrospinal fluid. (27 Refs)

39. DELAYED RECOVERY OF PERIPHERAL BLOOD CELL NUMBERS AFTER ADJUVANT CYTOTOXIC CHEMOTHERAPY FOR STAGE II BREAST CANCER.

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Cancer Chemother Pharmacol; 7(1):37-40 1981

Thirty women were given chemotherapy (CT) following mastectomy for breast cancer with axillary lymph node metastases. Fourteen patients received melphalan (MP: 0.15 mg/kg/day for 6 days, repeated for 1 yr; the dose was later increased to 0.2 mg/kg/day). Sixteen patients received melphalan and methotrexate (MT: 0.2 mg/kg on day 8 of each cycle). Doses were adjusted according to test results. All patients were observed for 2 yr after the end of treatment. Tumors recurred in 12 patients, who were withdrawn from the study. Peripheral blood cell counts (PBCC) of leukocytes, neutrophils, lymphocytes, monocytes, and platelets showed no differences between treatment groups at any time. PBCC for patients prior to CT differed from PBCC for normal patients only in having a lower mean number of monocytes. Counts of all cell types declined progressively during the first 6 mo of CT. Counts rose after CT was stopped but 36 mo later had not reached pretreatment levels. Results indicate that administration of MP in patients following mastectomy produces depression of hemopoiesis and lymphopoiesis lasting up to 3 yr. Consideration of this depression is urged, particularly in cases of early breast cancer, when expectation of long-term survival is high. Monitoring of hematological function following CT is recommended to determine which CT regimens carry a risk of hematologic depression. (14 Refs)

40. THERAPEUTIC RESULTS IN CHILDREN WITH NON-HODGKIN'S LYMPHOMA TREATED ACCORDING TO THE STANDARD PROTOCOL (LSA2L2).

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Pediatr Pol; 56(9):1071-1077 1981

The results of chemotherapy of 16 children (12 boys and 4 girls, 1-14 yr old) with non-Hodgkin's lymphoma (NHL) are reported. Lymphoblastic B-cell lymphoma was diagnosed in four patients, lymphoblastic T-cell lymphoma in two, immunoblastic lymphoma in three, convoluted lymphoblastic lymphoma in one, Burkitt's lymphoma in three, malignant histiocytosis in one, type U NHL in one and other NHL in one. Two patients were in Stage I, two in Stage II, four in Stage III and four in Stage IV. Remission induction therapy consisted of cyclophosphamide (CP: 1,200 mg/square m (m2), day 1), prednisone (PR: 60 mg/m2, days 3-31), vincristine (VCR: 1.5-2.0 mg/m2, days 3, 10, 17 and 24), methotrexate (MTX: 6.25 mg/m2 intrathecally, days 5, 27 and 30), and rubidomycin (RBC: 60 mg/m2, days 12 and 13). Consolidation therapy, started 3-5 days after remission induction therapy, consisted of cytosine arabinoside (ara-C: 150 mg/m2 iv on 5 consecutive days of the wk for 4 wk), 6-thioguanine (6-TG: 75 mg/m2 po according to same schedule as ara-C), L-asparaginase (60,000 U/m2 iv), and lomustine (60 mg/m2 iv). Maintenance therapy consisted of 6-TG, CP, RBC, MTX, VCR and ara-C. The patients were followed up for 1-40 mo. The fate of one patient is unknown. Seven children died within 1-10 mo (av 4.5 mo): the cause of death was dissemination of the malignant process in four cases, associated complications in three. The other eight patients have been alive for 1-40 mo (av 13.5 mo). Six of these eight patients are in continuing remission, one is alive with recurrence, and another is under remission induction therapy. The most severe side-effects included bone marrow depression with pronounced leukopenia and granulocytopenia. The findings indicate that the LSA2L2 protocol used is very aggressive but prolongs survival. (13 Refs) (In POL)

41. EFFECT OF CENTRAL NERVOUS SYSTEM RADIOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA ON LYMPHOCYTE SUBPOPULATIONS AND INDICATORS OF LEUKOCYTE MIGRATION INHIBITION IN THE PERIPHERAL BLOOD.

Cesarz-Kruz E, Lukas A, Sroczynska M, Lukas W, Sonta-Jakimczyk D
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Pediatr Pol; 56(9):1003-1007 1981

The effects of polychemotherapy and prophylactic cranial irradiation (total dose 2,400 rads) on peripheral blood lymphocyte subpopulations and on leukocyte migration inhibition were studied in 17 children (15 mo to 17 yr old) with null-cell acute lymphoblastic leukemia compared with 30 healthy controls. During remission after induction chemotherapy but before cranial irradiation, the percentages of T, B and null cells were 23.70%, 18.58% and 60.60%, respectively, compared with 64.45%, 23.73% and 10.8% in the controls. The decreases in the T and B cell counts and the increase in the null cell counts compared with the controls were statistically significant. The leukocyte migration indices were 0.833-0.938 vs 0.419-0.625 in the controls. After cranial irradiation the percentages of T, B and null cells were 20.25%, 12.5% and 65.10%, respectively, and the leukocyte migration indices were 0.881-0.887. The depressive effect of the irradiation affected mostly the B cells, and caused no significant changes in the leukocyte migration inhibition. (27 Refs) (In POL)

42. IMMUNE RESPONSES IN CARCINOMA OF THE COLON AND RECTUM.

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J Med Soc NJ; 79(1):19-22 1982

Cell-mediated immunity (CMI) after surgery in patients with carcinoma of the colon (CC) or rectum (CR) was compared with CMI in normal patients. CMI was measured by leukocyte migration inhibition assays (Lmi) using KCl extracts of tumor tissue. Of forty patients without malignant lesions, infections, or therapy-induced immunosuppression who underwent elective surgery, 27 showed positive Lmi prior to surgery. Of these, 23 showed negative Lmi immediately after surgery; 4 were positive. Lmi turned positive in 10 patients by 30 days after surgery and in 9 patients within 60 days after surgery; Lmi remained negative after 60 days in 4 patients. Patients with CC showed significant positive Lmi against autologous tumor extracts prior to surgery and immediately afterwards. Lmi turned negative during the late postoperative period. Patients with CR showed no significant positive Lmi against autologous tumor extracts at any time. Neither CC nor CR patients showed positive Lmi against allogeneic tumor extracts at any time, suggesting that each tumor was immunologically distinct. Comparison of Lmi in 20 patients undergoing electrocoagulation of CR with Lmi in 20 patients undergoing abdominoperineal or lower anterior resection showed that electrocoagulation had no effect on cellular immunity. Results indicate that surgery and anesthesia have an immunosuppressive effect and that differences in survival between patients with CC and those with CR may be due to differences in immunocompetence. (8 Refs)

43. REACTIVITY OF GASTRIC CANCER PATIENTS IN LEUKOCYTE MIGRATION INHIBITION TEST TO 3M KCL EXTRACTS FROM GASTRIC TUMORS.

Kojima O, Oh A, Kitagawa N, Uehara Y, Nishioka B, Fujita Y, Majima S
1st Dept. Surgery, Kyoto Prefectural Univ. Medicine, Kawarama-chi, Kyoto, 602, Japan
Jpn J Surg; 11(6):413-421 1981

Relationship between the leukocyte migration inhibition (LMI) reactivity and the clinical status of patients with gastric cancer (GC) and cross-reactivities between patients with GC and patients with colorectal cancer (CC) were studied. Leukocytes form patients with GC and other malignant and non-malignant diseases of the gastrointestinal tract and from healthy controls were tested for LMI using five different, allogeneic 3M KCl soluble extracts from GC tissues. Normal range of migration index (MI) was 0.77-1.18 derived by calculation of the mean MI of 10 healthy controls with cancer extracts; MI not in this range were considered pathological. Using the LMI test with single tumor extract pathologic MI was found in 48% of 79 GC patients. MI was significantly less in patients with CC and other non-malignant gastrointe stinal diseases (NGD). In the LMI test, testing each blood sample with five different tumor extracts, 79% of GC patients were reactive. CC patients showed positive reaction, and no positive reaction showed NGD patients. Positive reactivity in GC patients was significantly higher than in other studied groups of patients. GC extracts had a wide range of cross-reactivity when compared with colorectal tumor extracts which showed a relatively restricted cross-reactivity. LMI test when tested by a panel mode appears to express cell-mediated immunity against tumor associated antigens of GC. (27 Refs)

44. A NEW HISTOLOGICAL CLASSIFICATION OF MALIGNANT LYMPHOMAS (LSG CLASSIFICATION) AND ITS SIGNIFICANCE.

Mikata A, Suchi T, Wakasa A, Kikuchi M, Namba K, Mohri M, Mori S, Tojima K, Watanabe S, Harigoya S, Itagaki T, Matsuda M, Kirino Y, Takagi K, Mikata A
Dept. Pathology, Keio Univ. Sch. Medicine, Tokyo, Japan
Nippon Ketsueki Gakkai Zasshi; 44(7):1401-1410 1981

Findings of the present work farther support the rationale of LSG classification in regards to clinical behaviors and therapeutic approaches as well as origin of cells and their functional specificities. As revealed in the present work, large cell type was a heterogenous group and it would be further subdivided in the future. We believe this classification is in value not only in Japan, but in areas where T-cell lymphomas predominate over B-cell tumors. (Author abstract) (24 Refs)

45. EFFECT OF DIFFERENT EPSTEIN-BARR VIRUS-DETERMINED ANTIGENS (EBNA, EA, AND VCA) ON THE LEUKOCYTE MIGRATION OF HEALTHY DONORS AND PATIENTS WITH INFECTIOUS MONONUCLEOSIS AND CERTAIN IMMUNODEFICIENCIES.

Szigeti R, Masucci MG, Henle W, Henle G, Purtilo D, Klein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Clin Immunol Immunopathol; 22(1):128-138 1982

Leukocytes from healthy Epstein-Barr virus (EBV)-seropositive (SP) subjects show significant migration inhibition (LMI) with EBNA (EBV-determined nuclear antigen)-containing extracts derived from nonproducer, EBV-genome-carrying cells, or presented in the form of partially purified EBNA-preparations. Additional EBV antigens, EA and VCA, presented in the form of induced cell extracts do not add any measurable increase to their response. Leukocytes from acute infectious mononucleosis (IM) patients, on the other hand, do not respond to EBNA, but they show a good response to induced EA- or EA and VCA-containing cell extracts. This is in accordance with known differences in EBV-antibody pattern in healthy SPs as contrasted to acute IM patients. Leukocytes from chronic mononucleosis patients resemble those from acute IM patients in their preferential EA/VCA and deficient EBNA response in the LMI test. Cells from four X-linked lymphoproliferative disease (XLP) patients showed complete absence of reactivity to PHA and to EBV a ntigens in the LMI test, showing a general defect in cell-mediated immune responses. Leukocytes from a group of patients with lymphoproliferative malignancies in remission and elevated EBV-antibody titers showed a variety of responses, resembling normal SP donors, or IM patients, or showing a complete unresponsiveness in the LMI test. (Author abstract) (41 Refs)

46. HAIRY-CELL LEUKEMIA: CLINICAL AND HEMATOLOGICAL PICTURE.

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Pol Tyg Lek; 36(41):1585-1587 1981

Hairy-cell leukemia (HCL) was diagnosed in five patients (1 man and 4 women, 31-78 yr old) during a 2-yr period. The initial tentative diagnosis were those of agranulocytosis, splenomegaly, aplastic anemia, and chronic lymphadenosis (2 cases). Splenomegaly was present in all patients, lymph node enlargement in one. Erythrocytopenia was found in three patients, borderline erythrocytopenia in one, thrombocytopenia in four, borderline thrombocytopenia in one, and granulocytopenia in five. Lymphocytoid hairy cells were found in three patients, monocytoid hairy cells in two. Hairy cells accounted for 60-98% in the peripheral blood and for 27-95% in the bone marrow. The bone marrow specimens obtained by needle biopsy were cell-rich in three patients, hypocellular in two. Sternal biopsy, performed in four patients, showed sclerosis in two cases, fibrosis in two. Alkaline phosphatase activity was found in 35-80% of the hairy cells, this percentage being subject to changes in the course of the disease. Nonspecific alpha-naphthylacetate esterase activity was found in a few hairy cells. Less than 10% of the hairy cells were able to form E rosettes with sheep erythrocytes in 4/5 patients, but this percentage exceeded 70% in one patient during the leukemic phase of the disease. (23 Refs) (In POL)

47. CONTRASTING PATTERNS OF PROTEIN KINASE ACTIVITIES AMONG NORMAL PERIPHERAL BLOOD LYMPHOCYTE SUBPOPULATIONS AND LYMPHOID CELL LINES.

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J Lab Clin Med; 99(1):56-63 1982

Human peripheral mononuclear cell suspensions were separated into E-rosette-positive (T cell) and E-rosette-negative (non-T cell) fractions and assayed for cAMP binding activity and histone and casein kinase activity, in the presence and absence of cAMP. Each of these activities was higher in E-rosette-positive than E-rosette-negative fractions. Cyclic AMP binding and histone kinase activities were further noted to be higher in T lymphoblastoid cell lines when compared to lines of non-T lymphoid cell origin. In addition, DEAE-cellulose chromatography revealed a qualitative contrast of isoenzymic composition of protein kinase from these cell lines. Cyclic AMP-independent casein kinase activity was high in both types of cell lines. These results suggest that high protein kinase activity is characteristic of T cells and may be related to their higher sensitivity to cAMP agonists in comparison to non-T cells. This study also provides further evidence for an association between increased cAMP-independent protein kinase activity and the transformed state, which has been noted for a variety of other cell types. (Author abstract) (30 Refs)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

48. ISOPRINOSINE AS AN IMMUNOPOTENTIATOR IN AN ANIMAL MODEL OF HUMAN OSTEOSARCOMA.

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Int J Immunopharmacol; 3(4):383-389 1981

Immunostimulating capacity of isoprinosine (ISO) was investigated in normal and human osteosarcoma (OS)-bearing hamsters. In vitro concanavalin A (Con A)-induced lymphocyte proliferation was increased over control levels at all ISO concentrations tested (10, 20, 50, and 100 ug/ml medium) in both control and OS-bearing animals and was greater in OS-bearing hamsters (58-107%) than in normal hamsters (23-49%). On days 1, 3, and 5 following in vivo administration of ISO (23 or 5 mg/kg, ip) in both normal and OS-bearing hamsters, in vitro Con A-induced lymphocyte proliferation and natural killer cytotoxicity were increased; levels returned to control values on day 7. Before treatment, monocyte chemotactic responsiveness (MCR) was significantly lower in the OS group than in the normal group. However, 1, 3, and 5 days following ip injection of 2 mg/kg of ISO in OS-bearing hamster, MCR was significantly enhanced compared to similar hamsters which received only saline. Results indicate that ISO produces a generalized enhancement of immune function in hamsters with OS and suggest that the drug may be beneficial to human cancer patients. (29 Refs)

49. BONE MARROW TRANSPLANTATION ACROSS MAJOR HISTOCOMPATIBILITY BARRIERS IN MICE. III. TREATMENT OF DONOR GRAFTS WITH MONOCLONAL ANTIBODIES DIRECTED AGAINST LYT DETERMINANTS.

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J Immunol; 128(2):871-875 1982

We studied the effect of eliminating T cells from donor grafts of mice in a system in which bone marrow was transplanted across major histocompatibility barriers. BALB/c bone marrow (added as a source of hematopoietic stem cells) combined with equal volumes of spleen cells (added as a source of GVHD-promoting cells) was pretreated in vitro with monoclonal anti-Lyt-1.2 or Lyt-2.2 plus absorbed rabbit complement before injection into C57BL/6 total-body-irradiated recipients. Functional activity of anti-Lyt monoclonal antibodies was determined in CML assay. Treatment with anti Lyt-1.2 plus C did not have any anti-stem cell activity, as measured by CFU-S assay, and protected recipients from the onset of lethal GVHD. Treatment with Lyt-2.2 plus C also did not reduce CFU-S; however, mice receiving treated marrow did develop GVHD and were all dead by 2 mo, as were untreated control mice. Surviving 'anti-Lyt-1.2 + C chimeras' demonstrated a high percentage of donor mononuclear cells in their peripheral blood. Similar results were obtained when C3H/HeN donor BMS was treated with monoclonal anti-Lyt-1.1 plus C and injected into C57BL/6 recipients. These findings show that monoclonal antibodies directed against determinants unrelated to Thy-1 can eliminate T cells in the presence of C and successfully protect transplanted mice from lethal GVHD. They also suggest that these anti-Lyt antibodies may be useful tools in determining subpopulations of T cells that contribute to the development of GVHD. (Author abstract) (24 Refs)

50. THE ORGANIZATION OF HEMOPOIETIC TISSUE AS INFERRED FROM THE EFFECTS OF 5-FLUOROURACIL.

Hodgson GS, Bradley TR, Radley JM
Biological Res. Unit, Cancer Inst., 481 Little Lonsdale St., Melbourne, 3000, Australia
Exp Hematol; 10(1):26-35 1982

Mouse bone marrow obtained one day after injection of 5-fluorouracil (FU) had a markedly diminished content of spleen colony forming units (CFUs) but retained its capacity to repopulate the marrow granulocyte-macrophage colony forming cell (GM-CFC) and CFUs compartments of 850 R irradiated hosts and had only a slightly reduced platelet repopulating ability (PRA). A significant correlation (r = 0.94, p less than 0.001) was observed between the content of high proliferative potential granulocyte-macrophage progenitor (HPP-GM-CFC) and the platelet and marrow GM-CFC repopulating abilities of bone marrow cell suspensions. Spleens of irradiated mice, injected with marrow from donors treated with FU between 1 and 7 days before showed an increase in colony numbers with time of sampling between 8-13 days after transplantation. In contrast, the colony counts observed in mice injected with normal bone marrow remained constant over that time interval. The colonies derived from bone marrow of FU treated mice grew faster than those from bone marrow of normal mice. Spleens obtained from irradiated mice, 10 days after injection of bone marrow derived from donors treated with FU 1 or 3 days before, showed only a few macroscopic surface colonies but when sectioned were found to contain large numbers of microscopic colonies, 80% of which were megakaryocytic. The results are interpreted on the basis of a clonal succession model of hemopoiesis with stem cells of varying proliferative potential and proliferation rates increasing as capacity for cell production decreases. (Author abstract) (26 Refs)

51. MECHANISMS OF SYNGENEIC TUMOR REJECTION; SUSCEPTIBILITY OF HOST-SELECTED PROGRESSOR VARIANTS TO VARIOUS IMMUNOLOGICAL EFFECTOR CELLS.

Urban JL, Burton RC, Holland JM, Kripke ML, Schreiber H
La-Rabida Univ., Chicago Inst., Univ. Chicago, Chicago, IL, 60649
J Exp Med; 155(2):557-573 1982

Several progressively growing variants of the UV-induced 1591 regressor fibrosarcoma are described and studies on changes in susceptibility of the variants to natural killer cells and to tumor-specific or cross-reactive T cell-mediated immunity are reported. Five to 10-wk-old female C3H/HeN mice from a colony of germ-free-derived animals and normal nude animals were used. Five of 1591 regressor fibrosarcoma were isolated from normal animals to determine the selective pressures that had been exerted upon the parental tumor by normal immunocompetent hosts. The variant tumor cell lines could neither induce nor be killed by tumor-specific lymphocytes, suggesting that selection had been exerted against tumor cells expressing the tumor-specific antigen. No selection against natural killer cell activity or against nonspecific T cell-mediated immunity appeared to occur because progressor tumor cells were highly sensitive to these types of effector cells and induced these effector cells more effectively than did the parental tumor. Nude mice were capable of generating natural killer activity in response to a challenge with progressor tumor cells, but were unable to mount a nonspecific T lymphocyte response. Progressor tumors grew at a significantly faster rate in nude animals than in normal mice. Tumor nonspecific T cell-mediated immunity may play a role in retarding tumor growth, but the absolute resistance of normal animals to progressive tumor growth critically depends upon the presence of T cell-mediated tumor-specific immunity. Neither NK cells nor nonspecific cytotoxic T lymphocytes appear to play a role in immunoselection against this tumor in normal immunocompetent hosts. (34 Refs)

52. HIGH-FREQUENCY GENERATION OF NEW IMMUNORESISTANT TUMOR VARIANTS DURING METASTASIS OF A CLONED MURINE TUMOR LINE (ESB).

Bosslet K, Schirrmacher V
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Int J Cancer; 29(2):195-202 1982

A metastatic variant of a chemically induced lymphoma (ESb) from a DBA/2 mouse was found to activate in syngeneic hosts specific anti-tumor cytolytic T lymphocytes (CTL) which recognized on the tumor a distinct tumor-associated antigen. Upon metastasis of a cloned ESb tumor line from a sc site to the spleen, the tumor cells which were originally sensitive to lysis by anti-ESb CTL became specifically immunoresistant. The development of immunoresistant variants after tumor-cell transplantation followed a defined kinetic and organ pattern: they were first detected in the spleen, then also in the liver and in t he late stage of tumor progression they were the predominant tumor type in all involved organs. No immunoresistant tumor variants were generated in immunoincompetent animals such as nude (nu/nu) mice. Immunoresistant variants also developed when immunosensitive ESb clones were inoculated into animals specifically preimmunized against ESb. In fact, these variants were the only type of cells eventually growing out from such animals causing death from metastasis in spite of the specific immune status of the host. The change of tumor antigen expression described here differs from antibody-induced antigenic modulation in that it is genetically transmitted and stable in tissue culture. The immunoresistant tumor variants which did not preexist in the starting, twice-cloned cell population represent a new type of immune escape variant. (Author abstract) (24 Refs)

53. DIFFERENT T-CELL SUBTYPES ARE ASSOCIATED WITH PATHOLOGICALLY DISTINCT FORMS OF MOLONEY LEUKEMIA VIRUS (M-MULV)-INDUCED LYMPHOMA.

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Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Int J Cancer; 29(2):163-167 1982

The T-cell enzyme markers, terminal deoxy-nucleotidyl transferase (TdT) and 20 alpha hydroxysteroid dehydrogenase (20 alpha SDH), were used to classify lymphomas induced by the Moloney leukemia virus (M-MuLV). Different subtypes of T cells were shown to be involved in different types of lymphoma. Thymomas were TdT-positive and grew as sc solid tumors at the site of inoculation. Spleen cells from mice with generalized lymphoma were of two types. In the majority of cases the lymphomas consisted of 20 alpha SDH-positive cells that homed to spleen and lymph nodes upon transplantation. In a few cases the cells of enlarged spleens were TdT-positive and, like the TdT-positive thymomas, could be transplanted as sc tumors. Thus, TdT-positive and 20 alpha SDH-positive T-cell lymphomas can be distinguished by their homing properties. Preleukemic thymus cells from M-MuLV inoculated mice can, after transfer to 400-R irradiated syngeneic hosts, induce new lymphomas by virus release or grow in an autonomous fashion in the recipients. Whether of donor or recipient type, these lymphomas are TdT-positive. In contrast, preleukemic bone marrow cells give lymphomas of donor type which are as heterogeneous for T-cell enzymes as are lymphomas induced by neonatal inoculation of M-MuLV. (Author abstract) (14 Refs)

54. TUMOR-INDUCED IMPAIRMENT OF T-CELL-INDEPENDENT B-CELL BLASTOGENESIS AND DNA POLYMERASE ACTIVITY.

Farrar WL, Elgert KD, Burger CJ
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Proc Soc Exp Biol Med; 169(1):127-134 1982

T-cell-independent B-cell blastogenesis and DNA polymerase activity in fibrosarcoma-bearing BALB/c mice were investigated. Lipopolysaccharide (LPS)-induced B-cell DNA synthesis and DNA polymerase alpha activity were inhibited by two distinct suppressor cells. Macrophages directly suppressed B-cell blastogenesis in a system containing only B cells and macrophages plus mitogen. Direct suppression of B cells by macrophages was a function of the in vitro concentration of macrophages used; inhibition was not mediated via soluble molecules. The abilities of normal and tumor-bearing host macrophages to modulate LPS-induced blastogenesis were functionally similar. Suppressor T cells had a negative regulatory influence on B-cell LPS responsiveness, and these effects were achieved via a soluble factor(s). These findings suggest that tumor-induced suppressor T cells and perhaps macrophage regulation may be manifested in both T-cell-dependent and -independent blastogenic cellular effects. Macrophages may have a minimal inhibitory role in tumor-bearing hosts with respect to T-cell-independent systems. (24 Refs)

55. ROLE OF H-2 ANTIGENS IN THE HOST RESPONSE TO METHYLCHOLANTHRENE-INDUCED TUMORS. I. IN VIVO STUDIES.

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Dept. Tumor Biology, Karolinska Institutet, Box 60 400, S-104 01 Stockholm, Sweden

Immunogenetics; 15(1):53-62 1982

H-2 loss variant sublines of a sarcoma (M-AS), induced by methylcholanthrene in an (A x A-SW)F1 mouse, were used to study the role of the MHC products in the recognition of MC-TSTA. The two reciprocal variant sublines (M-A and M-S) were found to express the TSTA of the original tumor as shown by cross-reactions in graft rejection experiments performed in (A x A-SW)F1 mice. In the A/Sn and A-SW mice the presence of the reciprocal parental H-2 antigens on the immunizing cells decreased the response against the tumor antigens. An admixture of lymphocytes derived from hyperimmune mice inhibited the outgrowth of the tumor cells. The growth inhibition was mediated by T cells and was H-2 restricted. Cells derived from hyperimmune syngeneic mice inhibited the outgrowth of the variant subline used for immunization but had no effect on the reciprocal variant subline. (Author abstract) (17 Refs)

56. EFFECT OF AZIMEXON (BM 12.531) ON MOUSE GRANULOCYTE-MACROPHAGE AND MONOCYTE-MACROPHAGE PROGENITOR CELLS.

Jeng JC, McCarthy KF, Chirigos MA, Weiss JF
Biochemistry Dept., Armed Forces Radiobiology Res. Inst., Bethesda, MD, 20014

Experientia; 38(1):132-134 1982

Treatment of mice with 25 mg/kg azimexon (BM 12.531) resulted in an increase in granulocyte-macrophage colony-forming cells (GM-CFC) in spleen and bone marrow after a transient depression in the cell populations. Bone marrow monocyte-macrophage colony-forming cells (MM-CFC) increased at 7 days after treatment, and splenic MM-CFC were least affected by azimexon treatment. The increase in granul ocytic and monocytic colony-forming cells may play a role in the previously reported protection by azimexon against radiation and drug-induced toxicity. (Author abstract) (20 Refs)

57. REJECTION MECHANISMS OF XENOGENEIC TUMOR GRAFT IN THE CHEEK POUCH OF HAMSTER.

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Dept. Surgery II, Faculty Medicine, Kyushu Univ., Fukuoka 812, Japan

Fukuoka Igaku Zasshi; 72(10):575-588 1981

Rejection of xenografts by hamsters immunized in the cheek pouches with murine tumor cells was studied. Methylcholanthrene-induced tumor cells implanted in the cheek pouches were quickly rejected in immunized hamsters. Cytotoxic activity (CA) was detected by an in vivo neutralization test using cells from immunized hamster but was not detectable by 51Cr-release assay. CA was detected in peritoneal exudate in immunized hamsters bearing peritoneal tumor transplants. A cyclophosphamide- and x-ray-resistant delayed footpad reaction (DFR) was produced soon after immunization. Cytotoxic antibody (CAB) appeared later after immunization than killer activity or DFR. Hamsters exposed to x-rays did not produce CAB but did completely reject tumor xenografts in the cheek pouches. Antibody-dependent cell-mediated CA (ADCC) could not be detectable with antisera from hamsters with increased CA. Results suggest that xenograft rejection is effected by lymphocytes responsible for DFR and cell-mediated CA as detected at the site of rejection; CAB and ADCC apparently play a minor, if any, role in xenograft rejection. (53 Refs) (In JPN)

58. DEFECTIVE T-CELL RESPONSE IN BEIGE MUTANT MICE.

Saxena RK, Saxena QB, Adler WH
Immunology Section, National Inst. on Aging, NIH, 4940 Eastern Ave., Baltimore, MD, 21224

Nature; 295(5846):240-241 1982

Defective T-cell response in beige mutant mice was studied. To examine the generation of alloimmune cytotoxic T lymphocytes (CTL) in beige mice, 50 mutant (bg/bg) and heterozygous control (bg/+) mice (H-2b) were immunized with a single ip injection of P815 (H-2d) tumor cells. Five mice from each group were killed at different time intervals after immunization and the anti-P815 cytotoxic activities were determined at various effector/target ratios in a 4-hr 51Cr release assay. Lytic units (LU) of alloimmune CTL activity were determined from the dose-response curves. CTL activity in bg/+ mice increased rapidly from day 5 and reached a peak value of 33 LU/10(6) spleen cells on day 11. CTL response was specific to P815 target cells and was not observed against syngeneic EL-4 cells. By day 17, the activity had declined considerably but a secondary challenge in vivo with 2.5 x 10(6) P815 cells increased the level of CTL in bg/+ mice observed 1 wk after the second challenge. Anti-P815 was markedly lower in bg/bg mice; the peak level of CTL on day 11 was 11 LU/10(6) spleen cells. Secondary immunization did not increase activity in bg/bg spleens. Analysis of variance showed that the difference in generation of CTL activity between bg/bg and control mice was highly significant. To compare the magnitude of the CTL defect in bg/bg mice with the natural killer (NK) cell defect, NK activity was quantified in spleen cell preparation derived from bg/bg and bg/+ mice. Results confirmed both the previously reported NK defect in beige mice and a marked beige mouse defect in generation of alloimmune T cell in vivo and in vitro. Results do not suggest that beige mice could be useful as a model of selective NK deficiency. (14 Refs)

59. CYCLOPHOSPHAMIDE PRETREATMENT IN TUMOR CRYOTHERAPY: A MURINE MODEL.

Cooper AJ, Powell JM, Perry S, Fraser JD
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Cryobiology; 18(6):577-584 1981

Following the protocol of Turk and Lagrange for selective potentiation of cell-mediated immunity, a single high dose of cyclophosphamide was given to inbred mice bearing sc tumors 3 days before cryosurgery. Cyclophosphamide pretreatment caused a rise in the rate of total tumor ablation and local recurrence was delayed. The dose response to tumor size, cyclophosphamide, and freeze parameters indicated that these effects were the result of synergistic rather than additive processes. Instances of metastatic tumor growth and immunologically mediated complications of cryosurgery were also lower when the cryosurgery was accompanied by cyclophosphamide pretreatment. (Author abstract) (10 Refs)

60. GENETIC REGULATION OF THE INTERACTION OF IMMUNOCOMPETENT CELLS.

Benacerraf B
Dept. Pathology, Harvard Medical Sch., Boston, MA
Nippon Ketsueki Gakkai Zasshi; 44(7):1256-1262 1981

Antigen presentation to T cells and certain critical cellular interactions in immune responses controlled by the major histocompatibility complex (MHC), and T cell suppressor circuits regulation are discussed. One set of genes which regulates specific immune responses is in the MHC of mammals. The other genetic control of immune responses resides in the germ line V genes of immunoglobulin H chains, which control the generation of antibody combining sites, the specificity of T cell receptors, and through the idiotypic network, the nature of feedback regulatory systems, involved in the control of specific immune responses. (30 Refs)

61. CANCER AND BEHAVIOR: CONJUGATED EFFECTS OF METHYL NITROSOUREA (MNU) AND CONDITIONED EMOTIONAL RESPONSE (CER) ON EXECUTION OF A PROGRAM OF VARIABLE INTERVAL (VI) AND ON DEVELOPMENT OF NEOPLASIAS IN RATS.

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Facultad de Patologia, Universidad de Santo Tomas, Bogota, Colombia
Rev Latinoam Psicol; 13(3):375-401 1981

Of 12 male Wistar rats trained in a program of variable interval until they reached a stable state, 3 received methylnitrosourea (MNU: in 3 different doses), 6 received conditioned emotional response (CER) and MNU (in three different doses), 1 received saline soln, and 2 received CER and saline soln. Total rate of response was proportional to the dosage of MNU. Rats which received CER before MNU developed only medullary neoplasia (medulloblastoma or spongioblastoma), showed less cellular immunity to tumors and more development of neoplasia. Temporal discrimination of subjects, motivation, effects of CER and MNU and their interaction were analyzed. Location of neoplasia was spinal medulla (5), peripheral nervous system (2), and gastrointestinal mucosa (2). Types of tumors observed were medulloblastoma (2), spongioblastoma (3), neurinoma (2), and intestinal adenocarcinoma (2). (54 Refs) (In SPA)

62. T LYMPHOCYTES OF YOUNG AND AGED RATS. II. FUNCTIONAL DEFECTS AND THE ROLE OF INTERLEUKIN-2.

Gilman SC, Rosenberg JS, Feldman JD
Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
J Immunol; 128(2):644-650 1982

Splenic T lymphocytes of aged Lewis rats respond to Con A and PHA with diminished 3H-TdR uptake compared with splenic T lymphocytes of young Lewis rats. After immunization with allogeneic tumor cells, uptake of 3H-TdR in mixed lymphocyte-tumor cultures and T cell cytotoxicity against tumor target cells are significantly lower with spleen cells of aged rats compared with those of young rats. The culture of spleen cells of aged rats with Con A results in a diminished conversion of Ia-positive T cells from Ia-negative precursors compared with similar cultures of spleen cells of young rats. Spleen cells of both young and aged rats produce high amounts of IL-2 in response to Con A stimulation. 'Old' T cells, however, bind relatively little IL-2, do not utilize it in culture, and do not response to exogenous IL-2 with enhanced 3H-TdR uptake as do 'young' T cells. In allogeneic MLTC, 'old' T lymphocytes produce little IL-2 compared with 'young' cells, and both 'young' and 'old' cells respond to exogenous IL-2 with enhanced 3H-TdR uptake and increased cytotoxic activity. The data suggest defects in the synthesis and/or recognition of IL-2 as well as defects in the regulation of Ia antigen expression may be responsible, in part, for the reduced T cell function in aged animals. (Author abstract) (45 Refs)

63. REACTIVITY OF TUMOR-INFILTRATING, BLOOD, SPLEEN AND LYMPH NODE LYMPHOCYTES AGAINST SYNGENEIC GLIOMA TARGET CELLS.

Stavrou D, Bilzer T, Anzil AP, Hulten M, Kaldrymidou E
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Anticancer Res; 1(3):125-133 1981

Pleomorphic gliomas were induced in inbred Fischer rats by administration of N-methyl-N-nitrosourea in drinking water and a permanent cell line (78FR-G-219) was established from the primary tumor. Lymphocyte-mediated reactivity was investigated in glioma-bearing rats. Cytotoxic and inhibiting responses of lymphocytes were compared and related to the tumor growth rate and tumor mass at different time intervals. Discontinuous Percoll density gradients were used to enrich tumor-infiltrating lymphocytes (TIL) and Ficoll-Isopaque flotation was used to enrich blood lymphocytes (PBL), spleen lymphocytes (SL), and lymph node lymphocytes (LNL). The reactivity spectrum of isolated lymphocytes raised against cultured

78FR-G-219 cells was monitored by the lymphocyte microcytotoxicity test and colony inhibition assay. A reduction of reactivity of PBL, SL and LNL was observed in tumor-bearing rats. TIL exhibited no natural killer (NK) activity, no cytotoxicity against syngeneic 78FR-G-219 cells and no colony inhibition in mixed lymphocyte/target cell cocultivation. In TIL, NK activity was slightly reduced against target cells of a noncross-reacting syngeneic astrocytoma cell line, 78FR-G-299. These results demonstrate a specific interaction between T cells and pleomorphic glioma cells. (37 Refs)

64. THE MECHANISM OF GENETIC RESISTANCE TO MAREK'S DISEASE IN CHICKENS.

Powell PC, Lee LF, Mustill BM, Rennie M
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Int J Cancer; 29(2):169-174 1982

Genetic resistance to Marek's disease in RPL line-6 chickens is expressed not only at the level of host immunological responses against virus and tumor antigens, but also at the level of target lymphoid cells for virus infection and transformation. The nature of the target cell involved was investigated. Spleen cells from susceptible line-7 chickens adsorbed more Marek's disease virus and turkey herpesvirus in vitro than line-6 spleen cells. In the case of Marek's disease virus this was reflected in the replicative ability of the virus in vivo. Transplantation of thymus fragments from 1-day-old line-7 chickens into thymectomized line-6 chickens conferred a high degree of susceptibility on the latter, but the transplantation of spleen or bursa fragments had no significant effect. The reverse procedure, ie grafting of line-6 thymi into line-7 chickens, did not diminish the susceptibility of the recipients. In each treatment group the observed titers of leukocyte-associated viremia correlated with the susceptibility of the group to Marek's disease. Histologically the grafted thymus fragments became depleted of lymphocytes immediately after transplantation. By 6 days there was substantial recovery, apparently as a result of repopulation of the thymic epithelium by host stem cells. This was confirmed by transplanting thymus fragments between individuals of opposite sexes. Karyotype analysis showed that the thymus contained lymphocytes of the sex of the recipient. However, karyotype analysis of lymphoma cells taken from recipient line-6 chickens that had received thymus grafts from line-7 birds of the opposite sex showed that, in the majority of cases, the lymphomas consisted of cells of donor origin. It is concluded that the susceptibility of line-7 chickens is largely attributable to the greater susceptibility of their T-lymphocytes to infection and transformation by Marek's disease virus, and that this susceptibility can be transferred to genetically resistant line-6 birds by adoptive transfer of the cells in the form of thymus fragments. (Author abstract) (16 Refs)

65. SYNGENEIC AND ALLOGENEIC CELL-MEDIATED CYTOTOXICITY AGAINST MAREK'S DISEASE LYMPHOBLASTOID TUMOR CELL LINES.

Schat KA, Shek WR, Calnek BW, Abplanalp H
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Int J Cancer; 29(2):187-194 1982

Cell-mediated cytotoxicity (CMC) of lymphocytes obtained from chickens infected with Marek's disease (MD) virus against allogeneic MD lymphoblastoid cell lines has been reported by several research groups. Recently, we established a number of cell lines from MD tumors obtained from highly inbred chickens and characterized for major and minor histocompatibility antigens. Allogeneic versus syngeneic CMC was studied using those cell lines and lymphocytes obtained from chickens 6-8 days post infection with SB-1, a non-oncogenic MD virus. Allogeneic cytotoxicity could be easily demonstrated, while syngeneic cytotoxicity was a rare event. However, increase of the CMC assay period from 4 to 8 hr did enhance syngeneic cytotoxicity. Cold inhibition assays demonstrated that the allogeneic cytotoxicity was directed against alloantigens present on spleen lymphocytes sharing the same major histocompatibility antigens as the target cells. Cytotoxicity was not influenced by the sex of either target or effector cells or by the level of virus infectivity of the effector cells. (Author abstract) (32 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

66. THE IMMUNOSUPPRESSIVE EFFECT OF MONOCLONAL ANTI-LYT-1.1 ANTIBODIES IN VIVO.

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Eur J Immunol; 11(12):1005-1012 1981

Monoclonal anti-Lyt-1.1 alloantibody was produced as tissue culture supernatant and administered to mice. The antibody, given intraperitoneally, resulted in the suppression of all T cell functions studied, but was without direct effect on B cells. Thus, skin and tumor allograft survival was prolonged and there was suppression of the delayed-type hypersensitivity response; T cell help in the anti-sheep red blood cell antibody response, responder cells in the mixed lymphocyte reaction (MLR), leuko agglutinin-responsive cells, cytotoxic T cell (Tc) function and the induction of Tc were either totally or partially suppressed, all these responses being mediated by Lyt-1+2- or Lyt-1+2+ cells in CBA/H mice. By contrast, there was no inhibitory effect on the MLR-stimulating or lipopolysaccharide-responsive cells. The administration of the anti-Lyt-1.1 antibody was accompanied by a depletion of Lyt-1.1+ T cells from both spleen and lymph node. These studies indicate that the monoclonal anti-Lyt1.1 antibody is active in vivo with a selective effect on T cells. The results also have important implications for studies of T cell interactions in the mouse in vivo, and for similar studies in man. (Author abstract) (26 Refs)

67. MONOCYTE-INDUCED HUMAN NATURAL KILLER CELL SUPPRESSION FOLLOWED BY INCREASED CYTOTOXIC ACTIVITY DURING SHORT-TERM IN VITRO CULTURE IN AUTOLOGOUS SERUM.

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Scand J Immunol; 14(5):555-563 1981

When normal human peripheral blood mononuclear cells were tissue-cultured in autologous serum under conditions permitting cell contact, spontaneous fluctuations in cytotoxic activity were found. An analysis demonstrated that monocytes have the capacity to suppress initially (Days 1-2) natural killer (NK) activity and that, at later time points (Days 3-7), cytotoxic activity against the NK-susceptible target cell Molt-4 occurs which increases above initial NK levels. The newly induced killing depended on adequate cell contact for its induction and correlated with spontaneous proliferation in the cultures. The monocyte-induced NK suppression was found to be independent of cell contact and inhibited by the presence of indomethacin, thus most probably mediated by secreted prostaglandins. Suppressed NK cells (at Day 1) had a lower number of target-binding cells (TBCs) and a smaller fraction of active NK cells among TBCs as compared with control cells. The fluctuations in cytotoxicity as seen in the present in vitro system are discussed in relation to clinical conditions with decreased NK activity, such as multiple sclerosis and Hodgkin's disease. (Author abstract) (30 Refs)

68. BEHAVIORALLY CONDITIONED SUPPRESSION OF A GRAFT-VERSUS-HOST RESPONSE.

Bovbjerg D, Ader R, Cohen N
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Proc Natl Acad Sci USA; 79(2):583-585 1982

The compound, cyclophosphamide (CY), previously used to condition suppression of humoral immune responses, was used to condition suppression of a graft-vs-host response (GvHR). Female (Lewis x Brown Norway) F1 rats were conditioned by pairing consumption of a saccharin solution with an intraperitoneal injection of CY at 50 mg/kg of body wt 48 days before immunization. On day 0, all animals were injected with a suspension of splenic leukocytes (2 x 10(7) cells per footpad) obtained from female Lewis donors. The regional GvHR was assessed on day 5 by weighing popliteal nodes. Conditioned animals given a single low-dose injection of CY and reexposed to conditioned stimuli had lymph node weights significantly lower than control groups and did not differ from animals given three injections of CY during the ongoing GvHR. The results suggest that conditioned immunosuppression, previously demonstrated in thymus-dependent and thymus-independent humoral immune responses, also affects the popliteal GvHR, a cellular immune response. (Author abstract) (26 Refs)

69. PURIFICATION OF A LYMPHOID CELL LINE PRODUCT WITH LEUKOCYTE INHIBITORY FACTOR ACTIVITY.

Meshulam DH, Blair HE, Wong BL, Charm S, Minowada J, Rocklin RE
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Proc Natl Acad Sci USA; 79(2):601-605 1982

Leukocyte inhibitory factor (LIF), a lymphokine that inhibits the random and directed migration of polymorphonuclear (PMN) leukocytes, was purified from a human non-T, non-B leukemia cell line (Reh). From 10 liters of serum-free supernatant, 1.3 ug of protein with LIF activity was obtained by the sequential use of affinity chromatography with concanavalin A-Sepharose, hydrophobic chromatography with hexylagarose, and gel filtration chromatography. The specific activity of LIF recovered represented an 80,000-fold purification over that of the initial crude serum-free supernatants, and the preparation at that point was estimated to be 80-90% pure. To both assess the purity of the preparation and provide a further purification step, Reh LIF activity recovered by the above procedures was subjected to isoelectric focusing. One major stainable protein band was identified; its isoelectric point was pH 5.4-5.5. Gels run in parallel for recovery of biologic activity revealed only one region (pH 5.4-5.5) with ability to inhibit PMN leukocyte migration. Iodination of Reh LIF resulted in a loss of biologic activity, but isoelectric focusing of this material revealed one major 125I-labeled band (pH 5.1) and several minor bands. The coincidence of biologic LIF activity with one stainable protein band as identified by isoelectric focusing implies that the final product may be homogeneous. (Author abstract) (21 Refs)

70. REMOVAL OF THYMIC-DERIVED LYMPHOCYTES DURING PHERESIS PROCEDURES.

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Vox Sang; 41(5/6):287-294 1981

Measurements have been made of the absolute T-cell loss experienced by normal donors undergoing three methods of pheresis used for the preparation of platelets and/or granulocytes for transfusion. Filtration leukapheresis was associated with a mean loss per donation of 1.7 x 10(8) T cells. The technique of intermittent flow centrifugation platelet pheresis resulted in a mean loss per donation of 3 x 10(9) T cells. When this latter technique was utilized for leukapheresis, with hydroxyethyl starch and prednisone taken 12 hr before the donation, the mean loss per donation was 3.9 x 10(9) T cells. When an intravenous dose of dexamethasone at the commencement of the procedure was used instead of prednisone for leukapheresis by intermittent flow centrifugation, the mean cell loss per donation was 2.2 x 10(9) T cells. We have examined the immediate effects of these procedures on circulating T lymphocytes and their responsiveness to mitogens. The only change of significance was an increased responsiveness to phytohemagglutinin after leukapheresis of the lymphocytes of those donors who had received prednisone. Replacement of T cells appears to be inefficient in adult life and thus functionally important numbers of T lymphocytes may be removed by repeated pheresis procedures. Careful examination of the potential immunological and clinical consequences of repeated pheresis appears warranted. (Author abstract) (30 Refs)

71. T CELL-MEDIATED IMMUNOREGULATION OF EPSTEIN BARR VIRUS- (EBV) INDUCED B LYMPHOCYTE ACTIVATION IN EBV-SEROPOSITIVE AND EBV-SERONEGATIVE INDIVIDUALS.

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J Immunol; 128(2):575-579 1982

Infection with Epstein Barr virus (EBV) is accompanied by seroconversion and life-long persistence of the virus in B lymphocytes. During acute EBV-induced infectious mononucleosis, suppressor T cells become activated, which may provide an additional mechanism of host defense against the causatived agent. When cultures of lymphocytes from normal adults seropositive for EBV were stimulated with the B95-8 strain of EBV, purified B cells produced increasingly higher numbers of immunoglobulin- (Ig) secreting cells, whereas in co-cultures of autologous B and T cells a profound suppressor T cell activity inhibited further B cell activation after 10 to 12 days in culture. No such T cell-mediated inhibitory effect was seen in cultures of lymphocytes obtained from normal adults seronegative for EBV, indicating a correlation between the suppressor effect with evidence of prior immunity to this virus. The T cell-mediated suppression in patients with infectious mononucleosis is characterized by an early-acting inhibitory effect on B cell differentiation that is not specific in that all polyclonal B cell activators are inhibited, whereas in EBV-seropositive normal subjects suppression is delayed in time and affects only EBV-activated cultures. These data indicate that after infection with EBV, immunoregulatory T cells are generated that are capable of inhibiting further EBV-induced activation of autologous B cells and thus may provide an additional unique mechanism of host defense against persisting EBV-infected B cells. (Author abstract) (35 Refs)

72. PRELIMINARY CHEMICAL AND BIOLOGIC CHARACTERIZATION OF (FC)TRF: AN FC FRAGMENT-INDUCED T CELL-REPLACING FACTOR.

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J Immunol; 128(2):590-594 1982

Fc fragment stimulation of Lyt-1+2-T lymphocytes triggers release of a T cell-replacing factor, here called (Fc)TRF. Chemical and biologic characterization of (Fc)TRF has been undertaken to provide information for its comparison with other T cell factors. Preliminary chemical characterization by column chromatography and isoelectric focusing suggest (Fc)TRF activity resides in a class of acidic molecules that fall into two size classes of 58-60,000 daltons and 35-40,000 daltons. This factor is distinct from interleukin 2 (IL 2) as it has no T cell growth-promoting or costimulator activity, although it can also be generated by Con A activation of murine spleen cells. By these results (Fc)TRF has been defined as a unique T cell-replacing activity that promotes differentiation of B lymphocytes to antibody-secreting cells. (Author abstract) (25 Refs)

73. T CELL TOLERANCE IN MOLONEY-MURINE LEUKEMIA VIRUS (M-MULV) CARRIER MICE: LOW CYTOTOXIC T LYMPHOCYTE PRECURSOR FREQUENCY AND ABSENCE OF SUPPRESSOR T CELLS IN CARRIER MICE WITH MOLONEY-MURINE SARCOMA (M-MSV)-INDUCED TUMORS.

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J Immunol; 128(2):774-779 1982

Mice neonatally injected with Moloney-murine leukemia virus (M-MuLV) become permanent virus carriers and, in contrast to normal mice, fail to reject Moloney-murine sarcoma virus (M-MSV)-induced tumors as adults (progressor mice). Failure of tumor rejection has been shown to correlate with lack of T cell responsiveness of lymphoid cells from carrier mice in terms of tumor-specific cytotoxic T lymphocyte (CTL) generation in vitro and with failure to transfer protection against tumor growth in T cell-deficient mice. Since, in addition, lymphoid cells of carrier mice failed to suppress CTL generation in vitro by M-MSV-immune spleen cells, it was concluded that neonatal M-MuLV injection resulted in a state of T cell tolerance. Recent reports have suggested that carrier mice injected with M-MSV (progressor mice) generate suppressor cells that mediate enhanced tumor growth and inhibit CTL generation in vitro. In the present report, we fail to confirm these findings by demonstrating the following: (a) Neither carrier nor progressor spleen cells suppress the tumor protective effect of M-MSV-immune cells in T-deficient mice. (b) Progressor spleen cells fail to suppress M-MuLV-specific CTL generation by immune cells. (c) Spleens of carrier mice contain 100-fold lower M-MuLV-specific CTL precursors than do spleens of normal mice, and spleens of progressor mice contain over 1,000-fold lower CTL-precursor frequencies than do spleens of regressor mice. (d) Spleen cells from progressor mice fail to inhibit the clonal response of small numbers of CTL precursors in micro-mixed leukocyte tumor cell cultures. Thus, these results support the hypothesis that M-MSV tumor progression in carrier mice is due to reduction in virus-specific CTL precursor frequency and not to the generation of suppressor cells. (Author abstract) (36 Refs)

74. HELPER FACTOR PRODUCTION IN MURINE SECONDARY SYNGENEIC MIXED LEUKOCYTE REACTIONS.

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J Immunol; 128(2):817-822 1982

Culture supernatants of murine thymocytes or spleen cells responding in a secondary syngeneic mixed leukocyte reaction (SMLR) were studied for their biologic effects on cell-mediated immune responses in vitro. Such supernatants contained helper factor(s) that facilitated the development of alloantigen-specific cytotoxic T lymphocyte (CTL) responses from thymocyte precursors. Thymocytes, but not spleen cells, required activation by allogeneic effect factor (AEF) in primary culture in order to proliferate and produce biologically active mediator(s) during a secondary SMLR. The same culture supernatants possessed, in some instances, weak T cell growth factor (TCGF; IL 2) activity. However, TCGF activity could be dissociated from helper factor(s) active in the CTL induction assay because some culture supernatants that had potent helper activity were devoid of TCGF activity. This lack of TCGF activity was not due to a lower degree of sensitivity of the TCGF assay or to the presence of a selective TCGF inhibitor in the SMLR-derived supernatants, indicating that the helper factor(s) studied is distinct from TCGF. Production of immunoregulatory lymphokines during the SMLR may serve as a physiologically relevant model for studying the role of T cell-derived lymphokines in immunoregulation. (Author abstract) (41 Refs)

75. INHIBITION OF LEUKOCYTE MIGRATION BY HUMAN THYROID ADENOCARCINOMA ASSOCIATED ANTIGENS.

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Acta Endocrinol (Copenh); 99(1):56-63 1982

The agarose microdroplet leukocyte migration inhibition (LMI) assay was used successfully to demonstrate the existence of cell-mediated immunity to tumor-associated antigens (TAA) in patients with thyroid adenocarcinoma. With the use of crude tumor extracts obtained from a mixed papillary-follicular adenocarcinoma of the thyroid by hypertonic KCl solubilization, 50.0% positive reactivity was observed in metastatic thyroid cancer patients, whereas no healthy donors or patients with auto-immune thyroid disease showed a positive response in the LMI assay. Among responders, no antigenic cross-reactivity was found between the crude tumor extracts and non-cancerous antigens such as human thyroglobulin, or extracts of Graves' disease thyroid tissue, or kidney tissue. The crude tumor extracts were fractionated by Sephadex G-200 chromatography and the effluent materials were pooled into three fractions. The high mol wt fraction corresponding to the side of thyroglobulin elution, and the intermediate mol wt fraction, showed no TAA activity. The low mol wt fraction including substances of molecular size near that of ovalbumin (45,000 mol wt) selectively retained the TAA activity. TAA activity in the low mol wt fraction was concentrated in comparison to the crude tumor extracts. When this fraction was tested in the LMI assay, positive reactivity increased in metastatic thyroid cancer patients, but no response was observed in either healthy donors or patients with thyroid auto-immune diseases. The LMI response to TAA was more striking in patients with active metastatic cancer than in those whose metastatic foci had responded to treatment. (Author abstract) (24 Refs)

76. HUMORAL FACTORS INVOLVED IN THE MECHANISM OF REACTIVITY OF THE MICROPLATE LEUKOCYTE ADHERENCE INHIBITION ASSAY.

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Immunol Commun; 10(7):611-630 1981

To study if specific antigen(s)-induced adherence inhibition is due to direct cell contact or mediated by a soluble factor, spleen cells and enriched populations of B-cells and T-cells from normal C57Bl/6J mice and mice bearing progressively growing MCA-38 tumors were incubated with MCA-38 tumor antigen(s) and control B-16 melanoma antigen(s) for 1 hr at 37 C. The supernatants of these cultures were harvested and evaluated for their ability to induce adherence inhibition of normal peritoneal cells. Supernatants of MCA-38 sensitized B-cells but not T-cells could induce adherence inhibition of normal peritoneal cells. Furthermore, supernatants of MCA-38 sensitized spleen cells could not induce adherence inhibition of normal peritoneal cells, despite the fact that these cells can directly undergo specific antigen(s)-induced adherence inhibition. However, the sensitized spleen cells, after removal of the supernatant, were less adherent than comparable cells incubated with media alone, suggesting that the reactive cell within the spleen cell population adsorbed the soluble mediator as it was being generated. Affinity chromatography studies revealed that the biologically active soluble mediator contained IgG. Gel filtration studies indicated that the soluble mediator had a mol wt greater than 190,000 daltons. Thus, in this murine tumor model, leukocyte adherence inhibition is dependent upon the interaction between sensitized B-cells and specific tumor antigen(s) to produce a soluble mediator and is an antibody-mediated phenomenon. (Author abstract) (19 Refs)

77. APPEARANCE OF THREE LYMPHOKINES IN CULTURE SUPERNATANTS HARVESTED AT DIFFERENT TIMES.

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Immunol Lett; 4(1):21-26 1982

Factors responsible for WBC adherence inhibition (LAI), macrophage/WBC migration inhibition and acute erythrocyte-rosette augmentation (E-RA) were determined in culture supernatants of a fibrosarcoma induced in inbred CBA mice with 3-methylcholanthrene. Peritoneal cells from the mice were stimulated with the corresponding antigen and supernatants were prepared after incubation times of 1.0, 3.5, and 24 hr. Supernatants were tested by the indirect (two-stage) method on the same pool of indicator cells. The LAI inhibition factor was detected in both experiments in the 1 hr supernatant, in 1/2 at 3.5 hr, and not at all after 24 hr. The E-RA augmentation factor was found only in the 3.5 hr supernatant and the migration inhibition factor only in the 24 hr supernatant. Results indicate that the mediators responsible for the three in vitro reactions are different substances with different kinetics of production by stimulated cells. To assume only a single factor would involve consideration of a complex system of distinct inhibitors. (25 Refs)

78. ACTIVATION OF NATURAL CYTOTOXICITY OF HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS BY INTERFERON: A KINETIC STUDY AND COMPARISON OF DIFFERENT INTERFERON TYPES.

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Br J Haematol; 50(1):85-94 1982

Overnight incubation of human peripheral blood mononuclear (PBMN) cells with leukocyte interferon (leucocyte IFN) resulted in a two-five-fold increase in natural cytotoxicity (NC) against the erythroleukemic cell line K562. Fibroblast IFN, purified to homogeneity by zinc-chelate chromatography, stimulated NC to the same extent, while partially purified immune IFN was about twice as active. Upon gel filtration of immune IFN, NC stimulating and antiviral activity co-eluted. Treatment of PBMN cells with ammonium chloride buffer (AmCl) abrogated NC nearly completely. Incubation of AmCl-treated cells with leukocyte IFN resulted in a partial regeneration of NC. Kinetic studies revealed that this regeneration required only a short exposure to IFN followed by a longer incubation period. The data are interpreted as indicating that in the process of NC activation IFN mainly acts as a trigger for precursor cells to mature into cells with NC. (Author abstract) (26 Refs)

79. HUMAN INTERFERONS ALPHA AND BETA INHIBIT T-CELL-DEPENDENT AND STIMULATE T-CELL-I NDEPENDENT MITOGENESIS AND NATURAL CYTOTOXICITY: RELATIONSHIP TO CHROMOSOME 21.

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Cell Immunol; 65(2):366-372 1981

The effects of purified human interferons, interferon-alpha and interferon-beta, on immunocompetent cells were compared. Both types of interferon inhibited blast transformation to the T-cell-dependent mitogens phytohemagglutinin, concanavalin A and pokeweed mitogen with IFN-alpha being more potent than IFN-beta. B-Cell mitogenesis induced by Staphylococcus Cowan I was enhanced by both IFN preparations with IFN-beta being more potent than IFN-alpha. Both types of IFN enhanced natural killer cell activity with differences in the dose-response curves. The expression of the IFN-induced modulation of the mitogenic responses was shown to be associated with human chromosome 21. No such association could be demonstrated for the effect of IFN on natural killer cell activity. (Author abstract) (31 Refs)

80. EFFECT OF INTERFERONS ON PROTEIN SYNTHESIS IN HUMAN LYMPHOCYTES. ENHANCED SYNTHESIS OF EIGHT SPECIFIC PEPTIDES IN T CELLS AND ACTIVATION-DEPENDENT INHIBITION OF OVERALL PROTEIN SYNTHESIS.

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J Immunol; 128(2):828-833 1982

Lymphoblastoid and fibroblast IFN inhibited PHA stimulation of overall protein synthesis in human lymphocytes by ca 30%. Inhibiton occurred within the first 6 hr of PHA treatment and was not progressive. DNA synthesis at 48 hr was inhibited to the same extent. Overall protein synthesis in resting lymphocytes was not detectably inhibited by IFN concentrations up to 1,000 U/ml. Thus, inhibition of protein synthesis and subsequent reduction of cell proliferation by IFN require certain early events in mitogen activation. Resting lymphocytes were not unresponsive to IFN treatment, however. Two-dimensional electrophoretic analysis of newly synthesized proteins after IFN treatment showed enhanced synthesis of a specific set of eight peptides (I-peptides), which were shown to be synthesized in T lymphocytes. This enhancement was produced by both IFN-alpha and IFN-beta after 4 to 6 hr of exposure and was identical for all lymphocyte donors studied. After growth stimulation, IFN treatment produced no enhancements of additional peptides, although the original eight I-peptides were enhanced as usual. It is concluded that the biochemical activities of the I-peptides, which remain to be determined, cannot inhibit protein synthesis in resting lymphocytes, but may do so after mitogen activation, when the major physiologic restriction of lymphocyte protein synthesis is released. Alternatively, the I-peptides may be unrelated to regulation of protein synthesis but may be involved in viral protection or enhancement of NK activity. (Author abstract) (30 Refs)

81. CELLULAR ORIGIN AND INTERACTIONS INVOLVED IN GAMMA-INTERFERON PRODUCTION INDUCED BY OKT3 MONOCLONAL ANTIBODY.

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J Immunol; 128(2):585-589 1982

OKT3 monoclonal antibody, a human T cell mitogen, induced interferon production by cultured mononuclear cells at 10(-11) M concentrations. Interferon was secreted only under conditions wherein OKT3 was mitogenic, and production was correlated with cell proliferation. Thus, like mitogenesis, interferon secretion reached a peak 3 days after OKT3 stimulation, was inhibited by a factor(s) in human serum, and required 1,000x higher concentrations of Fab and F(ab')2 fragments of OKT3 for induction. The interferon was most likely of 'gamma' (immune) type, because pH 2 and 56 C treatments denatured it, whereas anti-alpha or -beta interferon antibodies did not. Mononuclear cells were fractionated into subpopulations that contained OKT4+ cells (helper/inducer T cells), OKT8+ cells (cytotoxic/suppressor T cells), and OKM1+ cells (monocytes) by combining sheep red blood cell rosetting and complement-mediated lysis using monoclonal antibodies against specific cell types. Both OKT4+ and OKT8+ cells proliferated upon OKT3 stimulation with the absolute requirement of OKM1+ cells. However, OKT4+ cells plus OKM1+ cells were necessary for the secretion of interferon. Studies with selective pretreatments with mitomycin C suggested that gamma-interferon was secreted by the OKT4+ cells and that the OKM1+ population subserved an accessory function. (Author abstract) (27 Refs)

82. INTERFERONS AND CANCER: THE END OF THE BEGINNING OR THE BEGINNING OF THE END.

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No affiliation given
Clin Oncol; 7(4):271-274 1981

Human interferon (IFN) and its role in cancer therapy are reviewed. IFN may act directly as a growth inhibitor by arresting cell division or indirectly through the immune system. IFN has been shown to stimulate lymphocyte cytotoxicity and enhance macrophage and natural killer cell activity. Three human IFN, alpha, beta, and gamma, have been identified. Alpha IFN are produced by WBC in response to challenge with virus; at least eight alpha IFN polypeptides with mol wt between 18,000 and 25,000 exist. Beta IFN are produced by fibroblasts stimulated by viral infections. Lymphocytes exposed to some immunostimulants can produce gamma IFN. Results of dose-toxicity studies with the genetically engineered subtype IFN alpha2 are described. The overall response rates for IFN alpha2 treatment of cancers where data are available on greater than 15 patients are: breast carcinoma (35%), multiple myeloma (40%), non-Hodgkin's lymphoma (50%), malignant melanoma (7%), and large cell cancer (0). Most of these patients had advanced recurrent tumors. In a non-randomized study of patients with early osteogenic sarcoma, the 3-yr survival rates for IFN-treated and control patients were 69% and 34%, respectively. Although the results with IFN appear to be discouraging, conclusions should not be drawn since the range of tumors evaluated to date is small, only im administration of IFN has been studied, and no clinical series has determined the role of IFN in combination with existing cytotoxic agents. (19 Refs)

83. NATURAL CYTOTOXICITY TO MURINE CYTOMEGALOVIRUS-INFECTED CELLS MEDIATED BY MOUSE LYMPHOID CELLS: ROLE OF INTERFERON IN THE ENDOGENOUS NATURAL CYTOTOXICITY REACTION.

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Infect Immun; 35(1):5-12 1982

Lymphoid cells from unstimulated normal C57BL/6J mice were shown to lyse murine cytomegalovirus (MCMV)-infected syngeneic mouse embryo fibroblasts but not uninfected mouse embryo fibroblasts. This cytotoxicity by mouse effector cells was not restricted to MCMV-infected syngeneic cells. The effector cells mediating this cytotoxicity against MCMV-infected cells are similar to described natural killer (NK) cells mediating lysis of tumor cells and virus-infected cells. Because of the described augmentation of NK activity by interferon, we examined the role of interferon in the NK reaction. Although low levels of virus-induced interferon were detectable in supernatants of MCMV-infected mouse embryo fibroblasts, no interferon was detectable in supernatants of MCMV-infected rat heart fibroblasts, a target significantly more sensitive to NK cytolysis than infected mouse embryo fibroblasts. We were able to augment the NK reaction against MCMV-infected cells by in vitro treatments with interferon. The amounts of interferon required for augmentation were significantly greater than the amounts generated by infected target cells. In vitro interferon-stimulated NK cells retained selective cytotoxic activity since they continued to remain incapable of lysing uninfected target cells. MCMV-infected rat heart fibroblasts induced more interferon and were also more susceptible to NK activity than MCMV-infected mouse embryo fibroblasts. In spite of this difference in interferon-inducing capacity, there was no augmentation of cytotoxicity of MCMV-infected mouse embryo fibroblasts when mouse splenocytes were cocultivated with both target cells. Finally, when production of interferon in the NK reaction was inhibited by the addition of actinomycin D, no reduction of NK activity was seen. Our findings suggest that native mouse NK cells can discriminate between MCMV-infected cells and uninfected cells, this ability leading to the selective lysis of the virus-infected cells. Furthermore, although we could demonstrate augmentation of NK activity by interferon, interferon activation of NK cells may not be a necessary precondition for the development of endogenous NK activity. (35 Refs)

84. ANTITUMOR EFFECT OF TUFTSIN.

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Mol Cell Biochem; 41:13-18 1981

Tuftsin, a physiological tetrapeptide derived from the Fc region of leukophilic IgG possesses a variety of immunopotentiating properties including the ability to act as an immunotherapeutic agent against the experimental tumors, L1210 leukemia and Cloudman S-91 melanoma. Although the mechanism of action of tuftsin in vivo is not known, several types of leukocytes have been shown to become cytotoxic effector cells following activation with tuftsin. These cells presently include macrophages, natural killer cells, and granulocytes. The possibility that tuftsin can also activate other types of effector cells has not been ruled out. We feel this small peptide has a high potential (largely unrecognized) as an antitumor immunopotentiating agent. It is naturally occurring in man and appears to be relatively non-toxic. Its exact sequence (Thr-lys-Pro-Arg) is known and it can be chemically synthesized. Methods are also available to monitor the levels of tuftsin in body fluids. These properties along with its ability to control infectious disease make this agent one of the more promising immunopotentiators. (Author abstract) (28 Refs)

85. TILORONE, ITS ANALOGS, AND DEVELOPMENTS IN CHEMICAL IMMUNOLOGY.

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Ing Chim; 63(300):45-53 1981

Characteristics of tilorone, a broad spectrum antiviral agent and inducer of interferon, are presented. Tilorone exerts effects upon both antibody and cell-mediated immune responses and has the paradoxical property of stimulating antibody production while simultaneously suppressing T-lymphocyte function. In common with other immunomodulators, tilorone shows a wide spectrum of activity against a variety of experimental and human tumors. Topics discussed include immunobiology, immunopharmacology, antiviral activity, interferon, cancer, enzymes and molecular biochemistry, and microbiology and immunogenetics. (no Refs)

86. COMPARATIVE EFFECTS OF AZATHIOPRINE CYCLOPHOSPHAMIDE AND FRENTIZOLE ON CELLULAR IMMUNITY IN MICE.

Smith SR, Terminelli C, Kipilman CT, Smith Y
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J Immunopharmacol; 3(2):133-170 1981

The immunosuppressive properties of cyclophosphamide (CPA), azathioprine (AP), and frentizole (FZ) were compared. Systemic graft vs host reaction (GVHR; splenomegaly assay) was complet ely suppressed in mice treated with AP (25 mg/kg) or CPA (5 mg/kg); FZ gave some suppression. When spleen cells from immunosuppressant-treated animals were injected into F1 hybrids systemic GVHR was inhibited by CPA (10 and 20 mg/kg), by AP (25 mg/kg), but not by FZ. AP and FZ (po) did not suppress local GVHR induced by injection of spleen cells into the left hind foot, but 5 mg/kg CPA (po) gave 70% suppression. The proliferative ability of spleen cells in irradiated A/J B6A hybrids was markedly suppressed in mice treated po or by ip injection with CPA or AP, but FZ had no effect. Only CPA prevented oxazolone-induced increase in lymph node wt in a dose-responsive way; FZ and AP had some weak effects. Spleen cells from mice treated with the three drugs showed varying responses when cultured with concanavalin A, phytohemagglutinin, or lipopolysaccharide. Spleen cells from C57BL/6 mice treated po with AP or CPA responded slightly to irradiated DBA/2J spleen cells, whereas cells from FZ-treated mice responsed normally. Murine sarcoma virus-induced tumors responded by some mass reduction in animals treated with AP and CPA po for 12 days after tumor induction. A single dose of 300 mg/kg of FZ or CPA actually enhanced tumor growth when administered 24 hr before virus inoculation. Oral treatment (21 days) with 25-50 mg/kg AP or 20 mg/kg CPA retarded Sal-spindle cell fibrosarcoma, but FZ had no effect. CPA, FZ, and AP can induce significant changes in some lymphoid tissues. CPA seems to be the most effective of the three drugs in suppressing cellular immune responses of mice. (32 Refs)

87. INDUCTION OF FCRALPHA ON MURINE LYMPHOCYTES BY IGA IN VITRO.

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J Immunol; 128(2):888-894 1982

The regulatory influence of IgA on the expression of Fc receptors specific for IgA (FcRalpha) on mouse spleen cells was studied. In normal BALB/c spleen cells, the proportion of FcRalpha-bearing (FcRalpha+) cells was less than 2%, determined by the rosette formation with IgA-coated sheep red blood cells (SRBC) or with trinitrophenylated (TNP) SRBC after incubation with soluble MOPC 315 IgA, which specifically binds with TNP. There was no marked increase of FcRalpha+ cells after 24-hr culture in IgA-free medium or treatment with acid pH (pH 5.0). When cultured with MOPC 315 IgA for 18 hr, there was a dose-dependent increase of the cells binding TEPC 15 IgA-coated SRBC as well as the cells forming rosettes with TNP-SRBC. Twenty to 30% of spleen cells expressed FcRalpha when cultured with 300 ug/ml IgA. The induced receptors bound both soluble IgA and IgA-coated SRBC, and proved to be specific for IgA by the inhibition with other isotypes. The induction of FcRalpha by IgA was inhibited by the inhibitors of RNA and protein synthesis (actinomycin, puromycin, cycloheximide), and required more than 8 hr of culture for the expression. Mitomycin (50 ug/ml) failed to inhibit the induction, indicating that proliferation of the cells is not required. FcRalpha was induced by dimer IgA but not by monomer IgA. Reduction of IgA with 0.02 M dithiothreitol resulted in the loss of inducing ability. However, reduced IgA competitively inhibited the induction of FcRalpha by nonreduced IgA and cytophilic binding of nonreduced IgA to the receptor. FcRalpha was induced by IgA on spleen cells depleted of adherent cells by Sephadex G-10 column passage. Both T and B lymphocytes were shown to express FcRalpha. (Author abstract) (34 Refs)

88. MECHANISM OF ENHANCED COMPLEMENT-DEPENDENT CYTOTOXICITY OF PAPAIN-TREATED LYMPHOCYTES: EVIDENCE FOR INCREASED STABILITY OF CLASSICAL PATHWAY C3 CONVERTASE.

Lublin DM, Grumet FC
(c/o Grumet) Dept. Pathology, L-235, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
J Immunol; 128(2):866-870 1982

The mechanisms of enhanced antibody-mediated, complement-dependent cytotoxicity caused by proteolytic treatment of cells was studied in a model system based on HLA microlymphocytotoxicity methods. In this model, papain treatment of lymphocytes resulted in (a) no change in antibody binding, (b) a slight decrease in initial binding of C4, (c) a marked increase in stability of cell-bound C4b, resulting in (d) an increase of cell-bound C3, and (e) no increase in lytic efficiency of the C5b-9 membrane attack complex. We conclude that the most important step in papain enhancement of lysis of lymphocytes is an increased stability of cell-bound C4b, possibly through decreased surface binding of C4-bp. This mechanism may be relevant to the pathologically increased lysis of cells occurring in patients with hereditary erythroblastic multinuclearity with a positive acidified-serum test (HEM-PAS). (Author abstract) (34 Refs)

89. CYTOTOXICITY OF L-CANAVANINE IN VITRO.

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Dept. Cell Biology, Christie Hosp. and Holt Radium Inst., Paterson Labs., Manchester M20 9BX, England
Anticancer Res; 1(5):275-277 1981

Cytostatic cellular reactions caused by L-canavanine (CAN) were studied in BALB/c-3T3 cells and phytohemagglutinin-stimulated human lymphocytes. BALB/c-3T3 cells were exposed to L-arginine (ARG) or CAN at concentrations of 1 x 10(-4) M, 1 x 10(-5) M, or 5 x 10(-6) M for 48 hr. Human lymphocytes were exposed to CAN at 1 x 10(-4) M to 1 x 10(-6) M for 50 hr at 37 C, then mitotic indices, karyotypes, and sister chromatid exchanges were studied. Of BALB/c-3T3 cells exposed to CAN for 48 hr then placed in growth medium without CAN, 90% treated with up to 1 x 10(-4) M recovered to continue DNA synthesis within 24 hr. Compared with ARG-treated cells, high labeling indices were observed after withdrawal of CAN, probably due to partial synchrony caused by CAN-induced inhibition of DNA synthesis. At lower concentrations (1 x 10(-6) M), the lower labeling index suggested partial inhibition and poorer synchrony. Cells exposed to 1 x 10(-4) M CAN for 48 hr recovered to form colonies as efficiently as untreated controls. In the presence of CAN, however, there was total inhibition of colony-forming ability. In the presence of CAN, few phytohemagglutinin-stimulated lymphocytes proceeded with mitosis, while mitosis continued when CAN (1 x 10(-4) M) was withdrawn. No difference in chromosomal aberrations or sister chromatid exchanges were noted between CAN treated and control cultures. (17 Refs)

90. AN ASSESSMENT OF THE CLASTOGENIC POTENTIAL OF 4-CHLOROMETHYLBIPHENYL IN HUMAN LYMPHOCYTES IN VITRO.

Richardson CR, Wildgoose J
Central Toxicology Lab., Genetic Toxicology Section, Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):287-293 1982

Clastogenicity of 4-chloromethylbiphenyl (4CMB) was studied in vitro in lymphocytes from four human donors. The lymphocytes were stimulated by phytohemagglutinin. 4CMB produced genetic damage in cells from 3/4 donors according to one criterion and in cells from 1/4 donors according to a second criterion. The most common defects produced were chromatid and chromosome gaps. Results indicate that 4CMB is clastogenic but only at concentrations that are cytotoxic. (3 Refs)

91. CONTRASTS BETWEEN THE RESPONSE OF THE MOUSE HAEMOPOIETIC SYSTEM TO 5-FLUOROURACIL AND IRRADIATION.

Dixon R, Rosendaal M
Dept. Anatomy and Embryology, Univ. Coll. London, Grower St., London WC1E 6BT, England
Blood Cells; 7(3):575-587 1981

Responses of the mouse hemopoietic system to 5-fluorouracil (5-FU), shielded-limb irradiation, and total-body irradiation plus bone marrow injection, and to a dose of 5-FU given 10 wk subsequent to each of these treatments, were studied. After 5-FU the numbers of spleen colony forming units (CFU) rose rapidly above normal levels 11 days after treatment, but the numbers of granulocyte-macrophage colony forming cells (GM-CFC) increased more slowly and remained subnormal. GM-CFC number reached normal 3-4 wk after partial-body irradiation or irradiation/reconstitution, although the CFU number rose slowly and did not reach pre-treatment levels. Two explanations for the difference are discussed; irradiation damages the hematopoietic environment in a way which prohibits fast proliferation of CFU, and 5-FU inhibits the differentiation of CFU into committed precursors. Two possible causes of artifact in CFU assays were investigated and corrected. The seeding efficiency of CFU, which varies according to cycling status, was adjusted by deducing cycling status from rate of change of CFU number. The second correction was for delayed colony formation by CFU after treatment with 5-FU. The response to a subsequent dose of 5-FU was the same in all groups, indicating that radiation damage to the stroma is either non-existent after 850 rad, or is repaired within 10 wk, or is irrelevant to the recovery from 5-FU. No difference was seen between the responses to partial-body irradiation and to transplantation. (25 Refs)

92. SPECIFICITY OF TUMOR CELL STIMULATION OF DNA INHIBITORY CYTOKINE PRODUCTION IN VITRO.

Kieler J, Houssini ME
Fibiger Lab., Ndr. Frihavnsgade 70, DK-2100 Copenhagen, Denmark
Anticancer Res; 1(4):235-241 1981

Spleen cell stimulation by ST/a lung fibroblasts which have undergone 'spontaneous' malignant alteration in vitro and the cellular subpopulation involved were studied. ST/a splenocytes and peritoneal macrophages sensitized to tumorigenic, isoimmunizing R+ ST-L cells in vivo produced a DNA inhibitory supernatant in vitro when co-cultured with R+ ST-L cells. Except for primary cultures of adult ST/a lung fibroblasts, all cells had a stimulatory effect on presensitized anti-R+ ST-L1 splenocytes relative to non-sensitized splenocytes. During the first passages the stimulatory effect of non-tumorigenic stimulator cells was significatnly lower than that of R+ ST-L1 cells, but in the 13th passage the difference disappeared. By studying cross-reactions with various uninfected and murine leukemia virus infected cells, evidence was obtained for gp 70 specificity of the stimulation. T-cell depletion and whole body irradiation caused a moderate reduction of the DNA inhibitory effect of the splenocyte culture supernatant. Macrophage depletion by silicate caused an almost complete abolition of DNA inhibitory cytokine production, which could not be restored by the addition of supplementary non-sensitized spleen cells. (25 Refs)

93. SENSITIVITY OF HUMAN NATURAL KILLER CELLS TO HYPERTHERMIA.

Azocar J, Yunis EJ, Essex M
Dept. Microbiology, Harvard Univ. Public Health, 665 Huntington Ave., Boston, MA, 02115
Lancet; 1(8262):16-17 1982

Significantly less natural killer (NK) activity is exhibited by human lymphocytes when the NK assay is carried out at temperatures above 37 C. Hyperthermia seems to act directly on the NK effector cells. The effect is partially abrogated by treatment of the heated cells with human leukocyte interferon. (Author abstract) (24 Refs)

94. PREOPERATIVE PARENTERAL FEEDING IN PATIENTS WITH GASTROINTESTINAL CARCINOMA.

Muller JM, Dienst C, Brenner U, Pichlmaier H
Dept. Surgery, Univ. Cologne, Joseph Stelzmann-Str. 9, 5 Cologne 41, W. Germany
Lancet; 2(8263):68-71 1981

In a comparative clinical trial to examine the influence of 10 days of preoperative parenteral nutrition (PPN) on the postoperative complication rate for gastrointestinal carcinoma 59 patients (controls) received the regular hospital diet and 66 received PPN. The two groups were similar in nutritional status and in distribution of site and stage of tumor and type of operation. The rates of postoperative wound infection, pneumonia, major complications, and mortality were generally lower in the PPN group, but the differences were significant only for major complications and mortality. The clinical results can be explained by the improvement in various indices of humoral and cellular immunocompetence and the protein status in the PPN group and their deterioration in the control group during the preoperative course. (Author abstract) (23 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

95. GROWTH DYNAMICS OF TRANSPLANTABLE GUERIN CARCINOMA AND MORRIS HEPATOMA IN RATS AFTER ADMINISTRATION OF A SINGLE BCG DOSE AT DIFFERENT TIMES.

Nowak HF, Cylwik B, Zimnoch L, Jodczyk KJ, Pregowski W, Duda D, Bernaczyk A
Zaklad Anatomii Patologicznej, Instytut Biostruktury Akademii Medycznej, ul. Kilinskiego 1, 15-089 Bialystok, Poland
Patol Pol; 32(2):173-184 1981

The effects of single sc doses of BCG vaccine (6 x 10(5) live cells), administered 7 or 2 days before tumor transplantation, on the day of transplantation, or 10 or 14 days after transplantation, on tumor growth dynamics and tumor morphology were studied in Wistar rats with transplanted Guerin carcinoma and in Buffalo rats with transplanted Morris hepatoma 5123. Results were evaluated 30 days after tumor transplantation. The mean wt of the Guerir tumors was significantly reduced in the rats vaccinated 2 days before transplantation and the mean wt of the metastases was significantly reduced in the groups vaccinated on the day of transplantation and 2 days before transplantation compared with the nonvaccinated controls. The mean survival time of the vaccinated animals did not differ significantly from that of the controls, but it reached 47 days in the group vaccinated on the day of transplantation. The mean wt of the Morris hepatomas and the av number of metastases per cubic cm lung tissue were significantly reduced in the group vaccinated 2 days before and on the day of tumor transplantation. Histological examinations of the vaccinated animals revealed proliferative reactions of macrophages and lymphocytes around the tumor cells, interaction of the histiocytes with the tumor cells, and retrograde and necrotic changes in Morris hepatomas and their metastases. (9 Refs) (In POL)

96. GAMMA INTERFERON PRODUCTION BY COMBINATIONS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES, MONOCYTES, AND CULTURED MACROPHAGES.

Arbeit RD, Leary PL, Levin MJ
Infectious Diseases Res., Medical Service, Veterans Admin. Medical Center, Boston, MA, 02130
Infect Immun; 35(2):383-390 1982

Mitogen-induced interferon (IFN) production was studied using human peripheral blood mononuclear cells and subpopulations of lymphocytes, monocytes, and cultured macrophages. Cell populations were prepared in suspension to permit quantitative analysis of the interactions among different cell types. After stimulation by staphylococcal enterotoxin A, nylon column-purified lymphocytes produced only 5% as much IFN as the peripheral blood mononuclear cells from which they were prepared. When lymphocytes were supplemented with as little as 2% monocytes, IFN production increased two- to eightfold; with the addition of up to 20% monocytes, IFN production increased further, to levels approximating those of peripheral blood mononuclear cells. Monocytes alone produced no or very little IFN. Macrophages were derived from monocytes by culturing in vitro for 7 days. The addition of 2 to 5% autologous macrophages augmented IFN production to the same extent as 2 to 5% monocytes. However, more macrophages consistently resulted in less, rather than more, IFN, so that lymphocytes with 20% monocytes produced three- to eightfold more IFN than did lymphocytes with 20% macrophages. Thus, whereas the addition of monocytes over a broad dose-response range (2 to 20%) progressively augmented IFN production, macrophages showed an optimal effect at 2 to 5%, with higher percentages being inhibitory. The IFN induced by stimulation with staphylococcal enterotoxin A was characterized as IFN-gamma by its resistance to neutralization by antibody to IFN-alpha and its inability to induce antiviral protection in embryonic bovine trachea cells. (Author abstract) (23 Refs)

97. ELEVATED CYTOSTATIC ACTIVITY OF MONOCYTES FROM CANCER PATIENTS.

Mashiba H, Matsunaga K, Yagawa K, Nomura Y, Yoshinaga H, Furusawa M, Jimi S
Div. Immunology, Natl. Kyushu Cancer Center, 595 Notame, Minami-ku, Fukuoka 815, Japan
Gan; 72(6):848-853 1981

Cytostatic activity of peripheral blood monocytes from patients with head and neck cancer, gastro-intestinal cancer, uterine cervical cancer, benign tumors of the head and neck, inflammatory diseases and pulmonary tuberculosis was studied by using a cultured lymphoid cell line as the target cell. Significantly higher cytostatic activities were observed at an effector-target cell ratio of 5:1 in these patients (except for pulmonary tuberculosis patients) than in healthy controls. The cytostatic activity of the monocytes from gastric cancer patients was more elevated in advanced stages than in Stage I. The cytostatic activity of culture supernatants of monocytes from cancer patients did not differ from that of healthy controls. The activity of the monocytes following radiation therapy combined with chemotherapy in patients with head and neck cancer was depressed. The significance of elevated cytostatic activity of monocytes in cancer patients is discussed. (Author abstract) (37 Refs)

98. GENERATION OF ENHANCED MACROPHAGE-MEDIATED ANTIBACTERIAL RESISTANCE IN ANIMALS RESPONDING TO TUMOR ALLOGRAFTS.

Newborg MF, North RJ
New England Coll. Osteopathic Medicine, 11 Hills Beach Road, Biddeford, ME, 04005
Infect Immun; 35(1):143-150 1982

Enhanced systemic antibacterial resistance was acquired by ACF1 (H-2ad) and B6D2F1 (H-2bd) mice bearing allogeneic BP-3 (H-2b) and SA-1 (H-2a) footpad tumors, respectively. This effect was dose dependent, in that the implantation of greater numbers of tumor cells produced larger tumors and higher levels of nonspecific resistance. Although the rejection of the tumor was T-cell dependent, the generation of nonspecific resistance was not. Thus, T-cell-deficient mice bearing progressively growing tumor allografts generated significant levels of antibacterial resistance. Two mechanisms were found to be involved in the generation of nonspecific resistance: (i) an acquired radioresistant mechanism responsible for initially destroying a large proportion of injected bacteria and (ii) an acquired radiosensitive mechanism responsible for destroying a significant number of bacteria after 24 hr. (Author abstract) (39 Refs)

99. FUNCTIONAL CHANGES OF MACROPHAGES FROM POLYOMA TUMOR-BEARING MICE.

Pituch-Noworolska A, Pajdak E
Div. Clinical Immunology and Microbiology, Inst. Pediatrics, Wielicka 265, 30-663 Krakow, Poland
Arch Immunol Ther Exp (Warsz); 29(4):423-429 1981

CBA mice were inoculated with different doses of polyoma tumor cells. The PHA response of spleen cells from tumor-bearers was decreased but the spontaneous incorporation of 3H-leucine was increased. PHA-induced cytotoxicity of spleen cells was increased only in tumor-bearers. The expression of Fc receptors showed a slight increase on adherent cells from spleen and peripheral blood mononuclear cells under suboptimal conditions for EA rosette formation (small amount of antibody for coating the erythrocytes). The non-specific esterase activity was assayed in an extract of peritoneal macrophages and the elevated activity with isoenzymes was seen in a group of tumor-bearers. The results suggest a functional alteration of macrophages in polyoma tumor-bearing mice. (Author abstract) (24 Refs)

100. IMMUNOCHEMOTHERAPY AND CYTOSTATIC ACTIVITY OF PERITONEAL MACROPHAGES IN TUMOR-BEARING RATS.

Irimajiri N, Saijo N, Ozaki A, Kimura K, Hashimoto N, Niitani H
Div. Internal Medicine, Natl. Cancer Center Hosp., Chuo-ku, Tokyo 104, Japan
Gan To Kagaku Ryoho; 8(Suppl):26-32 1981

The effect of BCG and/or 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2 chloroethyl)-3-nitrosourea (ACNU, NSC No D245382) on the cytostatic activity of peritoneal macrophages was examined in normal and tumor-bearing rats with special stress on the systemic effect of BCG. The correlation between the cytostatic activity of macrophages and tumor growth was also evaluated in tumor-bearing rats treated with BCG and/or ACNU. The decrease of cytostatic activity of macrophages induced by ACNU was prevented by the systemic administration of BCG. The systemic administration of BCG potentiated the effect of the anticancer agent in regard to tumor growth, and the elevated cytostatic activity of macrophages contributed to the suppression of tumor growth. (Author abstract) (13 Refs) (In JPN)

101. IN-VIVO MODULATION OF MACROPHAGE FUNCTIONS BY HERPES SIMPLEX VIRUS TYPE 2 IN RESISTANT AND SENSITIVE INBRED MOUSE STRAINS.

Armerding D, Mayer P, Scriba M, Hren A, Rossiter H
Sandoz Forschuagsinstitut G.m.b.H., Brunner Strasse 59, A-1235 Vienna, Austria
Immunobiology; 160(2):217-227 1981

Intra-peritoneal (ip) infection of mice with herpes simplex virus Type 2 (HSV 2) attracted macrophages into the peritoneum. Macrophages from moderately and highly HSV 2 resistant mouse strains expressed elevated phagocytosis activity 24 hours after injection. Stimulation of phagocytosis in low resistant strains was generally less effective or absent. This was, in some experiments, due to the fact that macrophages were already highly activated before the experimental infection. Ip infection also caused HSV replication in the adherent peritoneal exudate cell (PEC) population. The capacity of macrophages supporting HSV 2 replication was low in three of four resistant mouse strains and high in all moderately and highly susceptible and in one of the resistant (SJL) strains when determined 24 hours after infection. Four different F1 hybrids between resistant and susceptible strains exhibited significantly lower yields of virus-producing macrophages than the HSV-sensitive parent. One hybrid between two HSV-susceptible lines restricted virus replication in the PEC population better than both parental strains. (Author abstract) (25 Refs)

102. ANTITUMOR EFFECTS OF A VARIETY OF NON-VIABLE BACTERIA AGAINST THE MURINE EL-4 LYMPHOMA.

Mathews HL
Dept. Microbiology, Loyola Univ. Medical Center, 21360 First Ave., Maywood, IL, 60153
Cancer Immunol Immunother; 12(1):81-85 1981

Antitumor effects of non-viable bacteria were evaluated with EL-4 murine lymphoma in C57BL/6 mice using the bacterial species Staphylococcus aureus, Mycobacterium bovis (BCG), Propionibacterium acnes, Streptococcus mutans, Listeria monocytogenes, and Escherichia coli. Bacteria in varying amounts (10(8)-10(10) cells) were suspended with 1,000 EL-4 cells and injected id (0.2 ml) into the flanks of mice. Significant tumor suppression occurred in animals treated with all bacteria except

L monocytogenes; suppression of tumor growth depended on the number of bacteria injected. Multiple intralesional injection of the same kinds of non-viable bacteria yielded significantly increased survival in mice treated with four species but not in those receiving L monocytogenes or E coli. (30 Refs)

103. RADIOSENSITIVITY OF PULMONARY ALVEOLAR MACROPHAGE COLONY-FORMING CELLS.

Lin HS, Kuhn C, Chen DM
Div. Radiation Oncology, Mallinckrodt Inst. Radiology, St. Louis, MO
Radiat Res; 89(2):283-290 1982

The sensitivity of the reproductive integrity of pulmonary alveolar macrophage colony-forming cells (AL-CFC) to gamma irradiation was determined and compared to that of peritoneal exudate mononuclear phagocyte colony forming cells (PE-CFC). Only a small fraction of AL-CFC were found to be actively replicating in vivo, but could be made to proliferate in vitro after a long lag. AL-CFC were much more resistant to ionizing radiation than PE-CFC. (24 Refs)

104. FACTOR(S) RESPONSIBLE FOR THE INCREASE IN ALKALINE PHOSPHATASE ACTIVITY OF POSTMITOTIC GRANULOCYTES FROM NORMAL INDIVIDUALS AND PATIENTS WITH CHRONIC MYELOID LEUKEMIA.

Sato N, Mori M, Oshimura M, Ueymama Y, Miwa T, Ohsawa N, Kosaka K, Asano S
Third Dept. Internal Medicine, Univ. Tokyo, Tokyo 113, Japan
Blood; 59(1):141-147 1982

Using postmitotic granulocytes (PMGs) with low neutrophil alkaline phosphatase activity (NAP activity), factor(s) having the capacity to increase their NAP activity were examined in vitro. A high activity of the factor was demonstrated in the cystic fluid of a human squamous cell carcinoma, which is known to produce a large amount of granulocyte-macrophage colony-stimulating factor (GM-CSF). The NAP-stimulating factor increased NAP values both in PMGs from normal bone marrow and PMGs from patients with chronic myeloid leukemia (CML), and NAP values in cells treated with the factor approached or rose above those of normal peripheral granulocytes after 48 hr of culture. The effect of the factor was specific in that the factor caused stimulation only in granulocytic series. These findings may indicate that increases in NAP activity reflect maturation of granulocytes and that low NAP activity of neutrophils derived from patients with CML is due to the immaturity of these cells. The relationship between the factor responsible for the increase in NAP activity and GM-CSF is also discussed. (Author abstract) (34 Refs)

105. THE ACTIVATION OF CLONED MACROPHAGES BY CONCANAVALIN A FOR TUMORICIDAL EFFECT: ASSESSMENT OF TUMOR CELL CYTOTOXICITY BY A CLONOGENIC ASSAY.

Yen SE, Thomasson DL, Stewart CC
Div. Radiation Oncology, Malinckrodt Inst. Radiology, Washington Univ. Sch. Medicine, St. Louis, MO, 63110
J Cell Physiol; 110(1):1-8 1982

Activation of the tumoricidal effect of mouse peritoneal exudate cell (PEC) macrophages by concanavalin A (Con A) is described, and data relating to possible mechanisms of the tumoricidal effect are analyzed. Macrophage cells activated by Con A (greater than or equal to 20 ug/ml) were rounded and hypertrophied, whereas unactivated cells or those treated with alpha-methyl-D-mannoside (AMM; 0.01 M), a specific receptor-binding inhibitor of Con A, retained the stretched shape with pseudopods characteristic of normal macrophages. Con A at concentrations greater than or equal to 20 ug/ml activated cloned macrophages for cytotoxicity against EMT-6 BALB/c mammary adenocarcinoma cells in a dose- and time-dependent manner. Macrophage survival (number of adherent cells) decreased as concentration of Con A increased, except when cells were coincubated with 0.01 M AMM. The activated state of PEC macrophages declined after Con A removal, but greater than or equal to 50% of the cytotoxic activity remained present up to 4 days. A cytoxic fluid released by PEC macrophages, direct tumoricidal effects of Con A, contamination of Con A, and Con A-binding effects are discussed as possible causes of the cytotoxic effect observed, but the exact mechanism remains unknown. (42 Refs)

106. INHIBITION OF MONOCYTE COMPLEMENT RECEPTOR ENHANCEMENT BY LOW MOLECULAR WEIGHT MATERIAL FROM HUMAN LUNG CANCERS.

Glass EJ, Abell CA, Kay AB
(c/o Kay) Dept. Clinical Immunology, Cardiothoracic Inst., Fulham Road, London SW3 6HP, England
Clin Exp Immunol; 43(3):540-548 1981

We have studied the effect of dialysates from lung cancer homogenates to alter both the expression of complement (C3b) receptors per se and also to inhibit leucoattractant-induced enhancement of complement rosettes on monocytes from healthy individuals. Enhancement and enhancement-inhibition by tumor extracts were compared with material derived from normal lung excised some distance from the tumor. There was no significant difference between tumor homogenate (TH) and normal lung homogenate (NLH) in terms of enhancement of complement rosettes per se. In contrast, TH produced a dose- and time-dependent inhibition of leucoattractant-induced enhancement of C3b rosettes which was significantly different from that obtained with NLH. This enhancement-inhibition was observed with four undifferentiated, four squamous and three adenocarcinomas of lung. The degree of enhancement-inhibition was not related to the type of tumor or varying accompanying histological features such as necrosis and the degree of infiltration with inflammatory cells. Following gel filtration on Sephadex G-50 each type of cancer gave a major peak of inhibitory activity which eluted with molecules having an apparent molecular size of approx 3,000 daltons. A second larger peak (8,000-10,000 daltons) was also detectable with extracts from the undifferentiated and adenocarcinomas. These results support previous findings, mainly from experimental animals, indicating that 'anti-macrophage/monocyte principles' are elaborated from certain tumor types. (Author abstract) (20 Refs)

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY

107. THE CELL POPULATIONS MEDIATING NATURAL KILLING (NK) AND ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY ARE ONLY PARTIALLY IDENTICAL.

Bardos P, Altman J, Guillou PJ, Carnaud C
(c/o Carnaud) Inserm U 25, Hopital Necker, 161 rue de Sevres, 75015 Paris, France
Clin Exp Immunol; 43(3):534-539 1981

A cold target inhibition assay has been used to investigate the relationship between the effector cells responsible for NK and ADCC activity. Two models of ADCC have been studied in parallel with NK, one involving in vivo armed effector cells and the other involving normal effector spleen cells tested on antibody-precoated target cells. Bivalent effector cells active in ADCC and NK as well as monovalent NK cells and monovalent FcR-positive ADCC killer cells appear to exist concomitantly. However, the variability from experiment to experiment of the blocking efficiency displayed by the heterologous cold target, suggests that the proportions of monovalent to bivalent cells may vary between batches of mice depending on their immunological status at the time of the test. This should be taken into careful consideration when interpreting the results of this type of investigation. (Author abstract) (12 Refs)

108. EFFECT OF TREATMENT WITH GLUTAURINE ON HUMAN ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY (ADCC).

Lang I, Feuer L, Nekam K, Torok K, Kalmar L, Gergely P
Second Dept. Medicine, Semmelweis Univ. Medical Sch., H-1088 Budapest, Hungary
Immunol Commun; 10(6):499-509 1981

The effects of in vitro and in vivo treatment with glutaurine, a newly discovered parathyroid hormone possessing immunostimulative activity, on human antibody-dependent cell-mediated cytotoxicity (ADCC) were studied in 15 tumor patients and healthy subjects in a xenogeneic test system using chicken erythrocytes as target cells. A marked increase in 'K' cell activity was observed in eight tumor patients with originally low cytotoxic capacity, while originally normal ADCC activity of other tumor patients and healthy subjects was not significantly influenced by glutaurine treatment. The changes in cytotoxicity were not accompanied by changes in lymphocyte populations. Incubation of effector cells with glutaurine in vitro caused no change in ADCC activity in lymphocyte populations. Some similarities between the effects of glutaurine treatment on ADCC and that of dialyzable leukocyte extracts are discussed. (Author abstract) (33 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

109. CHARACTERIZATION OF E-ROSETTE-POSITIVE FC-RECEPTOR-BEARING CELLS BY FLOW CYTOMETRY.

Froelich CJ, Bankhurst AD, Warner NL
Dept. Medicine and Pathology, Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131
Clin Immunol Immunopathol; 22(1):105-117 1982

A subpopulation of human peripheral blood mononuclear cells which have the capacity to form spontaneous rosettes with sheep erythrocytes (E+) have been observed to also express a receptor for the Fc portion of immune complexed IgG. In this study quantitative flow cytometry is used to investigate the binding of human IgG to human E+ cells and to determine the relationship of these IgG-binding cells to the subsets of cells defined by OKT3 and OKM1 monoclonal antibodies. It was observed that a number of E+ cells bear an Fc receptor for monomeric human IgG; that all subclasses of IgG can bind to this subpopulation; that this subset overlaps with the T cell identified with rosetting techniques; and that virtually all of these E+ Fc receptor-positive cells binding monomeric IgG are phenotypically OKM1+ and OKT3-. (Author abstract) (19 Refs)

110. TTHETA-AND TGAMMA-CELL SUBSETS IN NORMAL AND LEUKEMIC CATTLE.

Surovas V, Pieskus J, Tamosiunas V, Sadauskas P
Inst. Biochemistry, Acad. Sciences Lithuanian S.S.R., 232021 Vilnius, Mokslininky 12, USSR
Thymus; 4(1):31-43 1982

T-cell subsets in the blood and lymphoid organs of normal and chronic lymphocytic leukemic cattle were examined; the T-cells bore receptors for IgM (Tmu) and IgG (Tgamma). Bovine Tgamma cells were more susceptible to the leukemic process than Tmu cells, acquiring enhanced adhesive properties during the process. (32 Refs)

111. IMMORTALIZATION OF ANTIGEN SPECIFIC, HELPER T CELL LINES BY TRANSFORMATION WITH THE RADIATION LEUKEMIA VIRUS (RADLV).

Yefenof E, Azar Y, Eidelsztein P, Ben-Sasson SZ
Lautenberg Center General and Tumor Immunology, Hebrew Univ-Hadassah Medical Sch., P.O.B 1172, Jerusalem, Israel
J Immunol; 128(2):625-628 1982

Antigen-specific immune T lymphocytes of male C57BL/6 mice were enriched in vitro on monolayers of antigen-pulsed syngeneic macrophages. The cells were treated in vitro with RadLV and inoculated intrathymically into irradiated female C56BL/6 animals. Thymomas arising in the inoculated recipients were characterized as donor- (male) type according to their karyotype. In vivo and in vitro cell lines were established from the primary lymphomas, two of which (designated ROT/6.1 and ROT/6.2) were capable of providing antigen- (carrier) specific help in normal or preimmunized mice. None of the lymphomas could induce antigen-specific DTH reaction. Five months after their establishment, ROT/6.2 alone retained its carrier specificity. ROT/6.2 consisted mainly of Lyt-1+ cells, whereas the ROT/6.1 population was more heterogeneous and contained Lyt-1+, Lyt-2+, and Lyt-3+ cells. The carrier specificity of the latter may have been lost due to selection against the specific helper cells during prolonged passages. (Author abstract) (18 Refs)

112. MONOCLONAL ANTI-T CELL ANTIBODIES REACT WITH MYELOID AND MONOCYTIC LEUKEMIA CELLS (MEETING ABSTRACT).

Pilkington GR, Hunter S, Jacobs DJ, Jose DG
Cancer Institute, Melbourne, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Rabbit and monoclonal antisera to human myeloid leukemia cell, monocytic leukemia cells and human thymocytes have shown the existence of common T-cell/myeloid/monocyte antigens. For this reason, the specificity of a series of monoclonal antibodies to human T-cells (OKT1, 3, 4, 5, 6, 8, 9, 10 and 11) was tested by immunofluorescence (cytofluorograph) and complement mediated cytotoxicity against human myeloid leukemia and normal blood cells and leukemic cell lines. Normal human peripheral blood mononuclear cells reacted with OKT3 ('pan T-cell', mean 70%), OKT4 ('helper T-cell', mean 55%) and OKT5/8 ('suppressor T-cell', mean 20%) as previously reported. However, OKT3 reacted with the cell lines K562 (myeloid), RC2a and THP-1 (monocytoid) and U937 (macrophage) as well as with cells from 3/10 myeloid leukemia patients. OKT4 reacted with the cell lines HL60 (promyelocyte), RC2a and U937 and also with cells from 3/10 myeloid leukemia patients. OKT5 reacted with the cell lines K562 and THP-1. OKT1 ('pan T-cell') reacted with THP-1 and with myeloid and monocytic leukemia samples (2/6) as did OKT6 ('cortical thymocyte') (3/9). OKT10 ('common thymocyte') reacted with a range of leukemia cell lines (B-cell, pre B-cell and macrophage) as well as 3/8 myeloid leukemia samples. (no Refs)

113. IMMUNOGLOBULIN SECRETING B LYMPHOBLASTS GROWN AND CLONED FROM WITHIN TUMOUR TISSUE FROM MELANOMA PATIENTS (MEETING ABSTRACT).

Watson DB, Mackay IR
No affiliation given
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Experiments were designed to produce human monoclonal antibodies reactive with antigens associated with and specific to melanoma cells. The approach entailed the use of Epstein-Barr virus (EBV) to transform B lymphocytes into proliferating B lymphoblastoid lines which could then be cloned. As the most likely source of specifically tumor reactive B lymphocytes, the EBV was added to a cell suspension from freshly resected melanoma. In this way 5 B lymphoblastoid cells lines have been established from within the tumor tissue of four patients. It has been demonstrated that these Epstein-Barr virus nuclear antigen (EBNA) positive lines secrete immunoglobulin and the kinetics of growth and secretion have been established. Two of these lymphoblastoid lines secreted immunoglobulin reactive with fresh autologous melanoma cells as well as melanoma cell lines. These lines have been cloned and are currently being expanded with the intention of producing large amounts of monoclonal anti-melanoma cell antibody. It is of inte rest that in two patients EBNA-positive B lymphoblastoid cells grew spontaneously from primary cultures of tumor tissue without contact with exogenous EBV. In contrast to normal subjects, T lymphocytes from the peripheral blood of these two patients were completely unable to mount an induced cell-mediated response against autologous B lymphoblasts, findings which demonstrate a degree of T cell incompetence. (no Refs)

114. PATTERNS OF PROLIFERATION AND DIFFERENTIATION OF IRRADIATED HAEMOPOIETIC STEM CELLS CULTURED ON NORMAL 'STROMAL' CELL COLONIES IN VITRO.

Mori KJ
Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
J Radiat Res (Tokyo); 22(3):344-351 1981

Irradiated bone marrow cells were overlaid on normal, unirradiated 'stromal' cell colonies and the pattern of proliferation and differentiation of hemopoietic stem cells was followed in vitro. Eight-wk-old male DDY mice were used for bone marrow cell culture, and 10-12-wk-old mice of the same strain were used as recipients for the assay of hemopoietic stem cells (CFUs). Culture of the bone marrow cells resulted in formation of adherent cell colonies within 3 wk. On these colonies were overlaid bone marrow cells irradiated with various doses of x-rays. Results show that the number of CFUs was reduced only to 48% of the control value even after 300 R. The normal level was attained within 2 wk of irradiation. A slight increase in the number of granulocyte-macrophage percursor cells (CFUc) in the late period was noted in cultured 300 R-irradiated bone marrow cells. Proliferation of hemopoietic stem cells was supported, with the degree of stimulation depending on the starting cellular concentration. No significant changes were observed in the concentration of either CFUs or CFUc regardless of the dose of irradiation to overlaid marrow cells. A dose-dependent decrease in CFUs and CFUc was observed within the culture in which both stem cells and stromal cells were simultaneously irradiated. The balance of self-replication and differentiation of the hemopoietic stem cell may be affected only when the hemopoietic microenvironment is perturbed. (16 Refs)

115. IN VITRO REPOPULATION OF HAEMOPOIETIC STEM CELLS AFTER IRRADIATION.

Mori KJ, Kumagai K, Seto A, Ito Y
Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
J Radiat Res (Tokyo); 22(3):312-322 1981

The effect of x-irradiation on stem cell kinetics in vitro was studied in bone marrow cell culture. Eight-wk-old male DDY strain mice were used for bone marrow cell culture; 10-12-wk-old male mice of the same strain were used as recipients for assay of pluripotent stem cells (CFUs). Irradiation of the bone marrow suspension immediately before the start of culture caused a dose-dependent reduction in number of adherent cell colonies (ACC) formed/culture flask. Sensitivity of the bone marrow cells m easured by the ability to form ACC was within the range of sensitivity of normal bone marrow cells (NBMC) irradiated in vivo. Survival of CFUs showed a linear curve reduction, according to the irradiation dose, with a D0 of 88 +-11R, which is in the range of the in vivo sensitivity of NBMC. Irradiation of granulocyte-macrophage precursor cells (CFUc) with 85 R resulted in a 50% reduction in survival, but irradiation up to 255 R did not alter the survival further. Ten percent of CFUc survived the dose of 510 R. Survival of CFUs after 1 wk in culture was approx the same as immediately after irradiation. Recovery thereafter was max in the range 100-200 R-irradiation. Recovery of CFUc was poor in the culture of 50 R-irradiated cells. Increase in the concentration of CFUs was more rapid than the increase in total cell number. CFUs and CFUc in vitro reached near-normal levels 3 wk after irradiation. Concentrations of CFUs and CFUc were higher in the irradiated cultures than in unirradiated control cultures 3 wk after irradiation. (20 Refs)

116. DETECTION OF GENES CODING FOR HUMAN DIFFERENTIATION MARKERS BY THEIR TRANSIENT EXPRESSION AFTER DNA TRANSFER.

Chang LJ, Gamble CL, Izaguirre CA, Minden MD, Mak TW, McCulloch EA
(c/o McCulloch) Inst. Medical Science, Sch. Graduate Studies, Univ. Toronto, Toronto, Ontario M5S 1A8, Canada
Proc Natl Acad Sci USA; 79(1):146-150 1982

We have developed an assay for specific genes in DNA based on transient expression. DNA prepared from patients with acute myeloblastic or acute lymphoblastic leukemia or from the continuous leukemic cell line HL60 was transferred to LTA cells; 48-72 hr later, these recipients expressed hemopoietic differentiation markers as detected by monoclonal antibodies against My-1 (granulocyte specific) and OK-T3 (T-cell specific) using immunofluorescence. The efficiency of transfer was dose and time dependent. We found that genes not expressed in the original cells were expressed after transfer by using this assay. Restriction enzyme analysis showed that My-1 was not expressed with DNA that had been incubated before transfer with either HindIII or SalI but was present after digestion with either EcoRI or BamHI; after digestion of DNA with the same enzymes, OK-T3 expression was observed only in the HindIII-treated DNA. These studies indicate that DNA was transferred; this approach may provide an efficient method for detecting the activity of specific genes in the absence of selection. (Author abstract) (20 Refs)

117. IMMUNOGLOBULIN PRODUCTION IN HUMAN MIXED LYMPHOCYTE CULTURES: IMPLICATIONS FOR CO-CULTURES OF CELLS FROM PATIENTS AND HEALTHY DONORS.

Rumke HC, Terpstra FG, Huis B, Out TA, Zeijlemaker WP
Central Lab., The Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands
J Immunol; 128(2):696-701 1982

When human peripheral blood lymphocytes (PBL) are cultured in the presence of irradiated allogeneic lymphocytes, the resulting mixed lymphocyte reaction (MLR) leads to the secretion into the supernatant of substantial amounts of IgM and IgG, derived from nonirradiated responder B lymphocytes. Our data indicate that stimulation to Ig production by responder B cells may result from different types of interactions. First, B cells and monocytes among the irradiated stimulator cells activate T cells in the responder population, which in turn trigger responder B cells to produce Ig; second, 'responder' B cells activate irradiated 'stimulator' T cells, leading to a 'helper' signal, back to the responder B cells and leading to Ig production. The latter system is radiosensitive, because allogeneic T cells, irradiated at a dose of 4,000 rad or more, failed to induce Ig production by responder B cells. In some combinations of human allogeneic lymphocytes, the co-culture of the cells leads to inhibition of Ig production, both in the presence and in the absence of PWM. Thus, co-culture of allogeneic cells may cause 'positive' as well as 'negative' allogeneic effects. The implications of these findings for the interpretation of co-cultures that are aimed at establishing defects in lymphocytes from patients with, for example, immunodeficiencies, who fail to produce Ig in the presence of PWM are discussed. (Author abstract) (21 Refs)

118. DIFFERENCES IN THE MIGRATION OF B AND T LYMPHOCYTES: ORGAN-SELECTIVE LOCALIZATION IN VIVO AND THE ROLE OF LYMPHOCYTE-ENDOTHELIAL CELL RECOGNITION.

Stevens SK, Weissman IL, Butcher EC
Lab. Experimental Oncology, Dept. Pathology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
J Immunol; 128(2):844-851 1982

The migration of B and T lymphocytes in the mouse has been studied by using (1) short-term in vivo homing studies, and (2) an in vitro assay of lymphocyte binding to specialized lymphoid organ venules (post-capillary, high endothelial venules (HEV)) in frozen sections of lymph nodes and Peyer's patches. The homing characteristics of B and T cell populations are largely independent of their organ of origin. B cells from any source distribute preferentially to Peyer's patches, whereas T cells home preferentially to peripheral lymph nodes. This organ specificity of migration appears to be determined at the site of lymphocyte exit from the blood by selective recognition of organ-specific determinants on the endothelial cells of HEV. In addition, the in vivo tendency of B cells to migrate preferentially to the spleen, and of T cells to localize better in lymph nodes is confirmed. Th results indicate that, in a hypothetical situation in which an equal number of B and T lymphocytes localized in peripheral lymph nodes (or bound in vitro to peripheral node HEV), there would be about 2.5 B cells for every T cell in the mesenteric node, four to six B cells per T cell in Peyer's patches, and seven to nine B cells per T cell in the spleen. Comparison of these homing preferences with the distribution of B and T lymphocyte populations in situ suggests that selective lymphocyte migration may help determine the proportions of functionally distinct lymphocyte classes in particular lymphoid organs or sites of chronic inflammation, and thus may serve to influence the character of local immune responses. (Author abstract) (39 Refs)

119. NORMAL AND MALIGNANT HUMAN MYELOCYTIC AND MONOCYTIC CELLS IDENTIFIED BY MONOCLONAL ANTIBODIES.

Bernstein ID, Andrews RG, Cohen SF, McMaster BE
Pediatric Oncology Program, Fred Hutchinson Cancer Res. Center., Seattle, WA, 98104
J Immunol; 128(2):876-881 1982

Two cytotoxic IgM monoclonal antibodies reactive with human cells of myeloid origin are described. Each antibody was tested for reactivity with normal and malignant cells of myeloid origin by using immunofluorescent and cytotoxic assays. Antibody 5F1 defines a determinant expressed by peripheral blood monocytes and platelets. Antibody 1G10 detects a determinant expressed in high concentration on granulocytes and in low concentration on a subset of monocytes. Neither antibody reacts with peripheral blood lymphocytes, erythrocytes, or thymocytes. In bone marrow, 5F1 stains monocytic and nucleated erythrocytic cells, whereas 1G10 stains cells of the granulocytic lineage. Each antibody also reacts with subsets of acute nonlymphocytic leukemia cells. These reagents should be useful in delineating stages of normal and malignant myeloid differentiation. (Author abstract) (37 Refs)

120. IDENTIFICATION OF HUMAN CML TARGETS. HLA-B LOCUS (B12) ANTIGEN VARIANTS DEFINED BY CTL GENERATED BETWEEN B LOCUS-IDENTICAL (B12) RESPONDER-STIMULATOR PAIRS.

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J Immunol; 128(2):949-955 1982

The genetics of human CML targets were studied by seven CTL generated in combinations in which the responder/stimulator difference was limited to one (or two) HLA-A, -B, or -C antigens. Unstimulated peripheral blood lymphocytes were used as targets. CTL sensitized against antigens A11, Aw31, or B17 lysed all cells bearing the respective target from a large panel of cells from unrelated individuals. Hence, at least one CTL clone was directed against the HLA antigen molecule. However, all CTL also exerted cross-kill to cells not sharing the stimulating HLA antigen. For two CTL, the target of the cross-kill was not clarified. Five CTL were found where the cross-kill was directed against antigen HLA-B12 (Bw44 and Bw45). All these CTL were generated in R/S pairs identical for B locus antigens (Bw44/Bw35 heterozygotes). The individual CTL lysed different parts of the panel of B12-positive target cells. The interpretation is that these CTL detect subtypes of HLA antigens, but alternative possibilities are also considered. Four B12 subtypes are described, tentatively designated as B12-related CML targets. Identification of HLA-B-related CML targets represent CML 'typing' of HLA-antigenic differences that were not detected serologically. The subtypes can now be tested for their possible functional significance. (Author abstract) (68 Refs)

SUPPRESSOR CELL ACTIVITY

121. SPONTANEOUSLY INDUCED SUPPRESSOR CELLS IN VITRO: NON-SPECIFIC SUPPRESSION OF IN VITRO ANTIBODY FORMATION.

Kodama K, Kurashige S, Mitsuhashi S
Dept. Microbiology, Sch. Medicine, Gunma Univ., Showa-machi, Maebashi, Gunma 371, Japan
Microbiol Immunol; 25(11):1173-1189 1981

Characterization of nonspecific suppressor cells induced during in vitro culture of normal mouse spleen cells (SPC) is reported. When normal SPC cells from BALB/c mice were cultured and stimulated with sheep (S) RBC on day 0, 3, 5, or 7, the responsiveness of the cultured SPC declined gradually. When freshly prepared normal SPC were added to the culture on day 7 or 14 and were stimulated with SRBC, no plaque-forming colony (PFC) response was observed, although freshly cultured SPC responded to antigenic stimulation when they were cultured with SRBC in the absence of precultured SPC. Suppressor activity was found not to be associated with precultured SPC supernatant. Suppressor cells inhibited both the primary and secondary antibody-formation responses, and the suppression was antigen non-specific. Suppressor cells inhibited the response of allogeneic SPC regardless of histocompatibility differences. Possibilities for eliminating suppressor cells which interfere with immunotherapy of tumors is discussed. (16 Refs)

122. SELECTIVITY IN THE EFFECTS OF INDOMETHACIN ON BCG-ACTIVATED SUPPRESSOR CELL POPULATIONS.

Bennett JA, Kemp JD, Mitchell MS, Rao VS
Dept. Surgery, Albany Medical Coll. of Union Univ., ME Building 514, Albany, NY, 12208
J Immunopharmacol; 3(2):221-239 1981

Indomethacin (IND) and the related compounds salicylate (salicylic acid), aspirin, and RO3-1314 were tested on BCG-induced macrophage-like suppressor cells from the spleen (S) and their precursors from the bone marrow (BM) of female C57BL/6 mice. In vitro immunization of S cells with irradiated P815 mastocytoma was prevented by pretreatment of S donor mice with BCG. All four drugs, when added at the initiation of coculture, almost completely blocked the inhibition of immunization produced by BCG-stimulated cells. IND was most effective: it was inactive at concentrations less than 10(-7) M while at concentrations greater than 10(-5) M it was itself immunosuppresive. Exposure to IND throughout the immunization culture per iod was more effective in blocking suppressor cells than shorter exposure, and the later IND was added the less was its blocking effect. The inhibitory activity of BCG-induced splenic suppressor cells was primarily in the nylon wool-adherent cells; IND inhibited suppressor activity in both adherent cells and unfractionated S cells. BM cells from BCG-treated mice were twice as suppressive as those from normal mice, but IND was not as effective in blocking the suppressor effect as it was with S cells. Nylon wool-adherent BM cells were more immunosuppressive than nonadherent cells; cells from both normal and BCG-treated mice suppressed immunization of normal cells. Immunosuppressive ability of adherent BM cells from both normal and BCG-treated mice was partially blocked by IND. While suppression generated by nonadherent marrow from normal mice was partially blocked by IND, it was ineffective on BM cells from BCG-treated mice. (37 Refs)

123. IMMUNOSUPPRESSION IN PLASMACYTOMA: INDUCTION OF SUPPRESSOR CELLS.

Chen Y, Hwang LT, Heller P
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Clin Exp Immunol; 47(1):191-196 1982

Immunosuppression in BALB/c mice with plasmacytomas (PC) is, at least in part, due to increased suppressor activity of splenic adherent cells. A PC subcellular fraction rich in intracisternal A particles, previously shown to have an immunosuppressive effect in normal BALB/c mice, is now shown to exert this effect through the development of splenic suppressor cells. The splenic suppressor cells induced with this subcellular fraction were found to be radioresistant adherent macrophages that suppressed the immune response of normal splenic cells to sheep erythrocytes through a diffusible factor, but did not influence their polyclonal IgM secretion after LPS stimulation in vitro. These characteristics are identical to those of the naturally occurring suppressor macrophages in mice with PC. Whether the induction of suppressor cells is due to the intracisternal A particles themselves or a factor co-purified with them, remains to be established. (Author abstract) (24 Refs)

124. EFFECTS OF PARTIALLY PURIFIED INTERLEUKIN 2 IN VIVO ON LYMPHOCYTE POPULATIONS, CYTOTOXIC ACTIVITY TO TUMOUR CELLS AND SUPPRESSOR CELL ACTIVITY (MEETING ABSTRACT).

Hersey P, Bindon C, Edwards A, Bradley M, Murray E, McCarthy WH
No affiliation given
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

The in vivo effect of interleukin 2 (IL2) was studied in patients with advanced melanoma. IL2 was prepared by stimulation of blood lymphocytes with phytohemagglutinin (PHA) for 24-36 hr and partially purified by membrane chromatography. The clearance rate (T1/2) of IL2 from the circulation w as 22.5 min. Neutrophilia, lymphocytopenia and depletion of spontaneous cell mediated cytotoxicity (CMC), measured in 51 Cr release assays, were noted in the first few hr after injections. In the days following the injections of IL2, a number of changes were seen in blood leukocytes which included an increase in the percentage of E rosettes and fluctuations in CMC. The marked increase in CMC to allogeneic target cells seen after culture of lymphocytes in IL2 for 5-6 days was not seen in vivo. Instead reductions in CMC were observed at 2-3 and 8-9 days after the IL2 injections for periods lasting 2-7 days - the actual timing and duration of the reduction appeared autologous melanoma cells was seen 7 and 13 days after the injections and appeared to persist for 5-16 days depending on the dose of IL2. Suppressor activity measured in pokeweed mitogen stimulated cultures of B and T cells was in general raised after the IL2 injections but the timing of changes in the latter activity could be clearly related to changes in CMC. (no Refs)

125. STUDIES ON INDUCTION AND EFFECTOR FUNCTIONS OF CONCANAVALIN A-INDUCED SUPPRESSOR CELLS THAT LIMIT TCGF PRODUCTION.

Gullberg M, Larsson EL
Dept. Immunology, Univ. Umea, S-901 87 Umea, Sweden
J Immunol; 128(2):746-750 1982

The cellular mechanisms regulating TCGF production in Con A-stimulated cultures have been investigated. Normal spleen cells, activated by Con A for 24 hr, develop suppressive cells that inhibit de novo production of TCGF by fresh spleen cells. Effector cells mediating suppression are nonadherent, radioresistant, Lyt-2-positive T cells. The induction of suppressor cells is radiosensitive and it requires 18 hr. The kinetics of suppressor cell induction parallels very closely the termination of TCGF production in situ, suggesting the major importance of this mechanism in the control of TCGF production. Reculture of 24-hr Con A-activated cells in the absence of Con A for 24 to 72 hr results in a gradual loss of suppressive activity that can be recalled by readdition of Con A with the same kinetics found in fresh spleen cells. In addition, de novo production of TCGF is readily induced in such cultures upon restimulation with Con A, demonstrating that abrogation of TCGF-production in primary cultures is due to suppression and not to lectin-dependent killing of the TCGF-producing T cells. Measurements of suppressive activity and lectin-dependent cytotoxicity, in various populations of Con A-activated spleen cells, further distinguish these activities. Finally, the reduced suppressive activity of Con A-activated cells after expansion in TCGF excludes that suppressor cells act by absorption or removal of TCGF produced at normal rates. Direct, reversible suppression of TCGF-producing cells by T lymphocytes appears, therefore, to constitute a major mechanism by which cytotoxic T cell responses are regulated. (Author abstract) (23 Refs)

OTHER RELATED STUDIES

126. MONOCLONAL ANTIBODY SPECIFIC FOR HUMAN T ACUTE LYMPHOBLASTIC LEUKEMIA.

Deng CT, Chia J, Terasaki P, Billing R
Dept. Surgery, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Lancet; 1(8262):10-11 1982

A cytotoxic mouse monoclonal antibody (CALL2) was produced against a cultured T acute lymphocytic leukemia (T ALL) cell line 8402. Ascites fluid containing the antibody was cytotoxic to a titer of up to 1:100,000 against four of six cultured T ALL cell lines and against leukemia cells from seven of eight T ALL patients and one of five T chronic lymphatic leukemia patients. The antibody did not react with normal peripheral-blood T and B lymphocytes, monocytes, granulocytes, spleen cells, thymocytes, platelets, and other acute and chronic leukemia cells. The CALL2 antibody did not react with bone marrow stem cells of the myeloid series (CFU-C). This antibody may be useful for passive immunotherapy trials since it does not react with normal cells and is highly cytotoxic to T ALL cells. (Author abstract) (9 Refs)

127. EXPRESSION OF THY1, TL AND LYT ANTIGENS ON SPONTANEOUS LEUKEMIAS OF BALB/MO STRAIN OF MICE.

Strzadala L, Opolski A, Kisielow P
Dept. Tumor Immunology, Inst. Immunology and Experimental Therapy, Czerska 12, 53-114 Wroclaw, Poland
Arch Immunol Ther Exp (Warsz); 29(4):439-441 1981

The expression of Thy1, and Lyt antigens on spontaneous BALB/Mo leukemias has been studied. The results obtained thus far indicate that a majority of leukemias express TL antigen and differentiated Lyt phenotype. This observation and other findings demonstrating and existence of TL+ thymocytes with different Lyt phenotypes in normal thymus of young mice lends support for the hypothesis that TL+Lyt2+ phenotype defines this stage in the T cell differentiation pathway, which is particularly sensitive to leukemic transformation. (Author abstract) (6 Refs)

128. ULTRASTRUCTURE OF ADULT T-CELL LEUKEMIA/ LYMPHOMA.

Eimoto T, Mitsui T, Kikuchi M
Dept. Pathology, Fukuoka Univ. Sch. Medicine, Nanakuma 34, Nishi-ku, Fukuoka, 814-01, Japan
Virchows Arch [Cell Pathol]; 38(2):189-208 1981

Eighteen cases of adult T-cell leukemia/lymphoma (ATLL) in Japan were analyzed by electron microscopy and compared with 5 cases of B-lymphoma and well-established groups of T-lymphomas (4 cases of T-lymphoblastic lymphoma and 2 cases of Sezary syndrome). Five hundred cells in each case, categorized ultrastructurally as to the cellular size and nuclear shape, showed an essentially pleomorphic cellular distribution in ATLL in remarkable contrast with the monomorphism of B-'histiocytic', B-well-differentiated lymphocytic, and T-lymphoblastic lymphomas. Some B-lymphomas and Sezary syndrome also showed pleo morphism. Cases of ATLL were classified according to the predominant cells and degree of nuclear irregularity, which delineated a spectrum of node-based, peripheral T-cell neoplasms probably encompassing T-immunoblastic sarcoma, T-zone lymphoma, as well as multilobated T-cell lymphoma. The characteristic fine structure of ATLL, in comparison with that of B-lymphomas, included slight to marked nuclear irregularity with convoluted-shape predominance, a speckled chromatin pattern of the large cells, prominent lysosomes, and glycogen accumulation in addition to the difference in cellular distribution. Although T-lymphoblastic lymphoma and Sezary syndrome shared some of these features, the ultrastructural differentiation of ATLL from them seems to be possible. (Author abstract) (31 Refs)

129. ANALYSIS OF LYMPHOCYTE DIFFERENTIATION ANTIGENS WITH HYBRIDOMA MONOCLONAL ANTIBODIES.

Shiku H, Yamaguchi H, Furukawa K, Yamada K
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, Nagoya, Japan
Nippon Ketsueki Gakkai Zasshi; 44(7):1395-1400 1981

The procedure for the production and analysis of hybridoma monoclonal antibodies is described. An example of the initial screening of 18 clones which were tested on 6 different human target cells is presented. Two clones obtained from mice hyperimmune to human T cell type acute lymphoblastic leukemia cells are composed of IgM immunoglobulins; their reactivities to target cells detected by the immune adherence (IA) assay are discussed. CL1-67-4 is predominantly reactive to lymphocytic cells but shows no specificity on T cell or on T cell lineages. IA assay with CL13-29-1 showed more restricted reaction of the antibody with cell populations of lymphocytes. CL12-29-1 reacts with 10-20% of thymocytes and 2-5% of T cells in peripheral blood lymphocytes, which indicates it may detect a subset of T cell lineage. Preliminary data indicate that these clones may detect differentiation antigens on human lymphocytes. Distribution of human cells detected with monoclonal antibodies is presented. Application of the methodology in its present form has already resulted in the availability of monoclonal antibodies for histocompatibility and differentiation tests of human cell antigens. Improving selection methods for the desired clone, reducing clonal instability due to chromosomal loss, and some other technical problems remain to be solved. (7 Refs)

130. CLONAL CHARACTERISTICS OF CUTANEOUS T CELL LYMPHOMAS: CYTOGENETIC EVIDENCE FROM BLOOD, LYMPH NODES, AND SKIN.

Nowell PC, Finan JB, Vonderheid EC
Dept. Pathology/G3, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
J Invest Dermatol; 78(1):69-75 1982

Chromosome studies were done on mitogen-stimulated lymphocytes from one or more tissues (blood, lymph nodes, skin lesions) in 15 patients with mycosis fungoides or Sezary syndrome. A cytogenetically abnormal clone was found in 10 individuals, including 6 with data from several tissues. In four cases the same aberrant clone was identified in a skin lesion as well as in blood and/or lymph node. the abnormal chromosome patterns ranged from hypodiploid to hypertetraploid, and there was no evidence of unrelated karyotypically-altered lines at different sites. A 6q- chromosome, previously reported in acute lymphocytic leukemia, was found in two patients. The results support the concept that cutaneous T cell lymphomas (CTCL) are clonal disorders, presumably unifocal in origin, with the skin lesions populated by cells from the same neoplastic clone that involves lymph nodes and blood. (Author abstract) (17 Refs)

131. RECOGNITION OF HLA AND MINOR ALLOANTIGENS ON HUMAN TARGET CELLS BY ALLOSTIMULATED CYTOTOXIC EFFECTORS IN VITRO.

Pierson G, Elkins W
Dept. Pathology, Univ. Pennsylvania, Philadelphia, PA, 19104
Transplant Proc; 13(4):1901-1905 1981

Recognition of human WBC antigen (HLA) and non-HLA alloantigens by effector cells induced by the pooled allogeneic stimulation (PAS) technic was studied using peripheral blood lymphocytes (PBL) from five HLA-matched siblings (family W) and several unrelated normal individuals. Among the W sibling was a 36-yr-old man (EW) with moderately severe aplastic anemia who required weekly platelet and occasional blood transfusions from his four HLA-matched siblings. The response to PAS of effector cells from each of the four normal W sibs was analyzed against target cells from the other four. Two different pools were used. In no case was significant killing observed. Similar results were obtained using 12 other pairs of normal HLA-matched siblings among four other families. PAS induced effectors that recognized foreign HLA, but not minor alloantigens, on mitogen-stimulated target cells from normal individuals. In contrast to the four normal siblings, PBL from EW responded both to stimulation with the pool and to direct stimulation with sibling cells to generate significant killing against targets from each of the normal W sibs. Stimulation of PBL from EW with matched sibling cells caused cytotoxicity against the unrelated target LH20. In EW, the presence of the B7 antigen among the stimulating cells appeared sufficient for associative recognition of as yet undefined minor antigens segregating in the siblings and also found in LH20. Results indicated that effectors induced by the pool are specific for HLA antigens either as alloantigens or as restriction elements for minor alloantigens. (12 Refs)

132. THE RIDDLE OF HODGKIN CELLS.

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Abt. Hamalotogie, Medizinische Hochschule Hannover, Hannover, W. Germany
MMW; 123(48):1827-1828 1981

Characteristics of the first tumor cell cultures successfully established from biopsy material of patients with Hodgkin's disease are described. Testing for markers of differentiation revealed that the cell lines had antigenic properties similar to those of early myelo-monocytes. Although the cell lines were established from biopsy specimens of four patients, they possessed many identical characteristics, identical marker chromosomes, and common cytochemical features. One of the four cell lines was positive for an Epstein-Barr-virus (EBV)-induced antigen, and another cell line possessed EBV receptors. The cell lines were poor inducers of tumor growth in nude mice. (no Refs) (In GER)

133. NEW EPSTEIN-BARR VIRUS VARIANTS FROM CELLULAR SUBCLONES OF P3J-HR-1 BURKITT LYMPHOMA.

Heston L, Rabson M, Brown N, Miller G
(c/o Miller) Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Nature; 295(5845):160-163 1982

Correlation between biological properties and genome structure was examined in 29 subclones of HR-1 virus, an Epstein-Barr virus (EBV) mutant that does not immortalize lymphocytes or induce lymphomas. None of the 29 clones spontaneously released EBV DNA in an amount comparable to that of the parental line. Differences in viral DNA content correlated with lower levels of viral capsid antigen (VCA) clones. Enhanced VCA expression occurred in five clones that released large amounts of DNA after treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA). The subclonal viruses resembled HR-1 in lack of immortalization, cytotoxicity, and interference with transformation; unlike HR-1, they did not induce virus early antigen (EA) synthesis in Raji cells. Differences in the DNAs of nontransforming virus (HR-1 and its subclones) and two transforming EBV strains were found to involve at least six regions of the genome. HR-1 DNA differed from the DNA of cloned and transforming viruses in that it contained three or four size variants of EcoRI ABC het fragments. Possible involvement of the fragments in EA induction is noted. (22 Refs)

134. A QUANTITATIVE ULTRASTRUCTURAL STUDY OF PERIPHERAL BLOOD LYMPHOCYTES CONTAINING PARALLEL TUBULAR ARRAYS IN EPSTEIN-BARR VIRUS AND CYTOMEGALOVIRUS MONONUCLEOSIS.

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Dept. Pathology, Univ. Arizona Health Sciences Center, Tucson, AZ, 85724

Am J Pathol; 106(1):71-83 1982

In the normal peripheral circulation there exists a subpopulation of lymphocytes that is ultrastructurally distinct. This lymphocyte is identified with the electron microscope by the presence of cytoplasmic microtubule-like inclusions called parallel tubular arrays (PTAs) and contains Fc-receptors for cytophilic antibody. In this study, lymphocytes containing PTAs (PTA-lymphocytes) were quantified from serial peripheral blood specimens obtained from two patients with Epstein-Barr virus (EBV) mononucleosis and two patients with cytomegalovirus (CMV) mononucleosis. These data were then correlated with the clinical state of the patient. It was determined that both the percentage and absolute number of PTA-lymphocytes were highest during the acute phase of the illness. In follow-up specimens, three of the four patients' absolute lymphocyte count fell to within normal limits before the absolute PTA-lymphocyte count. In one patient, the absolute PTA-lymphocyte count was significantly elevated 13 mo after the initial clinic visit. Although the PTA-lymphocyte count was highest during the acute phase of the illness, there was no consistent correlation with the clinical state of the patient during follow-up. The estimation of absolute PTA-lymphocyte counts was determined to be valid after a morphometric analysis of the cellular areas occupied by PTAs during the acute and convalescent phases of the disease revealed no statistical differences. Electron microscopy was also performed on the peripheral blood of a patient with syphilis. Although a hematologic workup of this patient during the acute phase of his illness revealed a large number of atypical lymphocytes, electron-microscopic examination of the same specimen revealed both a normal number and a normal percentage of PTA-lymphocytes. The immunologic role of this ultrastructurally distinct third population (non-T, non-B) of lymphocytes, or 'killer cells,' in the course of infectious mononucleosis is discussed. (Author abstract) (62 Refs)

135. ADENOSINE DEAMINASE AND PURINE NUCLEOSIDE PHOSPHORYLASE ACTIVITIES OF VARIOUS CULTURED CELL LINES DERIVED FROM HUMAN HEMATOLOGIC MALIGNANCIES.

Hirose M, Minato K, Shimoyama M
(c/o Shimoyama) Section Hematology, Natl. Cancer Center Hosp., 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104, Japan
Jpn J Clin Oncol; 11(3):481-486 1981

Cells from 22 cultured cell lines derived from human leukemia and malignant lymphomas were lysed when growing exponentially, and analyzed for adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) activities in crude cell extract. Generally, T-cell lines had higher ADA activities (per million cells) than all other cell lines; lines P 12/Ichikawa and MOLT-3 were especially active. B-cell and myeloid lines had slightly higher PNP activities than T-cell lines, but the differences were not evident when activity was expressed on the bases of mg/cell protein. ADA and PNP activities were not correlated in these cell lines. With respect to ADA activity, cultured T-cells reflect the characteristic of their original target cells as being comparable to cortical thymocytes. ADA activity is therefore considered to be a good marker of the thymic T cell and its malignant counterpart. (31 Refs)

136. HIGH AFFINITY BINDING SITES ON PLASMA MEMBRANE OBTAINED FROM THE LYMPHOBLASTOID CULTURED 1301 CELL LINE FOR HIGHLY RADIOACTIVE SERUM THYMIC FACTOR.

Gastinel LN, Pleau JM, Dardenne M, Sasaki A, Bricas E, Morgat JL, Bach JF
INSERM U 25, Hopital Necker, 161 rue de Sevres, 75015 Paris, France
Biochim Biophys Acta; 684(1):117-126 1982

The interaction of the synthetic serum thymic factor (FTS, facteur thymique serique) with a plasma membrane preparation of human T lymphocytes from the lymphoblastoid T cell line 1301 was studied using 3H-labelled FTS (specific activity 120 Ci/mmol). The binding is temperature dependent and function of the concentration of both 3H-labelled FTS and membrane proteins. At 37 C, using 1 nM of 3H-labelled FTS a steady state is observed within 80 min. The binding is reversible, specific and saturable. Scatchard analysis reveals the existence of at least two binding sites with respective Kd of the order of 0.516 +-0.2 nM and 110 +-27.8 nM with concentrations of 0.186 +-0.045 pmol and 2.026 +-0.367 pmol per mg of membrane protein. (Author abstract) (36 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/120

AUTHOR INDEX WITH CITATION NUMBERS

Abell CA 106
Abplanalp H 65
Abugaber AA 19
Adachi M 87
Adar U 36
Ader R 68
Adler WH 58
Advani SH 28
Aggio MC 8
Ahrlund-Richter 55
Aiuti F 5
Akimova GV 6
Altman A 74
Altman J 107
Andrews RG 119
Angelini G 25
Anzil AP 63
Aoki N 75
Arbeit RD 96
Ardila R 61
Armerding D 101
Asano S 104
Asjo B 53
Azar Y 111
Azocar J 93
Babcock GF 84
Bach JF 136
Bankhurst AD 109
Bankhurst AD 47
Bardos P 107
Ben-Sasson SZ 111
Benacerraf B 60
Bennett JA 122
Bergolits VM 6
Bernaczyk A 95
Bernstein ID 119
Biasi G 73
Bicker U 14
Billiau A 78
Billing B 126
Bilzer T 63
Bindon C 124
Bjorkholm M 10
Bjorkholm M 26
Blaese RM 71
[illegible] 69
[illegible] 14
[illegible] 27
[illegible] 22
[illegible] 52
[illegible] 68
[illegible] 22
Bradley M 124
Bradley TR 50
Braun-Falco O 24
Bremner U 94
Breur B 120
Bricas E 136
Brown N 133
Bucci Sabattini 1
Burchardt K 46
Burg G 24
Burger CJ 54
Burns GF 16
Burton RC 51
Butcher EC 118
Calnek BW 65
Carnaud C 107
Carter CA 34
Cesarz-Kruz E 41
Chang LJ 116
Chang TW 81
Charm S 69
Chen DM 103
Chen Y 123
Chia J 126
Chieco-Bianchi 73
Chirigos MA 56
Chmielewska D 17
Ciepielewska D 40
Claeys H 78
Cohen N 68
Cohen SF 119
Collavo D 73
Cooper AJ 59
Cooper HL 80
Corvellec MR 19
Cousineau GH 19
Cylwik B 95
Czurko J 46
D'Ovidio R 25
Dardenne M 136
De Ley M 78
DeGroot LJ 75
Deng CT 126
Derghazarian C 19
Detrick-Hooks B 4
Di Montezemolo 33
Diehl LF 4
Diehl V 132
Dienst C 94
Dixon R 91
Dreskin HJ 81
Du Bois R 120
Duda D 95
Duros H 22
Dwyer JM 70
Easty DL 34
Edwards A 124
Eidelsztein P 111
Eijsvoogel VP 120
Eimoto T 128
Elgert KD 54
Elias L 47
Elkins W 131
Ellegaard J 32
Eremeev VS 6
Essex M 93
Fagnani R 80
Farrar WL 54
Fauci AS 4
Fekete B 11
Feldman JD 62
Feltkamp CA 7
Feltkamp-Vroom 7
Fenyo EM 53
Feuer L 108
Finan JB 130
Florez Beltran 61
Fraser JD 59
Froelich CJ 109
Fudenberg HH 48
Fujisawa T 15
Fujita Y 43
Furukawa K 129
Furusawa M 97
Gamble CL 116
Gangal SG 28
Gastinel LN 136
Geppert M 27
Gergely P 108
Gerrard TL 4
Ghogale SR 28
Gilman SC 62
Glass EJ 106
Goldrosen MH 76
Goldstein G 81
Goodyear MD 39
Greco RS 42
Green B 79
Grumet FC 88
Gu SQ 23
Guillou PJ 107
Gullberg M 125
Gutkowska J 17
Gyarmathy L 11
Hallak A 36
Halliday WJ 77
Hamawaki M 30
Hammarstrom L 9
Harada T 35
Harigoya S 44
Hartley CE 34
Hashimoto N 100
Hauptmann E 21
Haviernick S 19
Haynes BF 4
Heim ME 14
Heller P 123
Henle G 45
Henle W 45
Hersey P 124
Heston L 133
Hirose M 135
Hodgson GS 50
Hoffmann-Fezer 24
Hogarth PM 66
Holland JM 51
Holm G 10
Holm G 26
Holm G 9
Hooks JJ 4
Houssini ME 92
Howell JH 76
Hozumi M 38
Hren A 101
Hubbard RA 8
Huis B 117

Hulten M 63
Hunter S 112
Hwang LT 123
Irimajiri N 100
Itagaki T 44
Ito Y 115
Ivanyi P 120
Izaguirre CA 116
Jacobs DJ 112
Jeng JC 56
Jimi S 97
Jodczyk KJ 95
Johansson B 10
Jondal M 67
Jose DG 112
Kaldrymidou E 63
Kalmar L 108
Kan M 35
Kan T 35
Kato S 120
Katz AJ 70
Kay AB 106
Keller R 83
Kemp JD 122
Kersey JH 49
Kieler J 92
Kikuchi M 128
Kikuchi M 44
Kikukawa K 30
Kimura K 100
Kipilman CT 86
Kirino Y 44
Kisielow P 127
Kitagawa N 43
Klein E 20
Klein E 55
Klein G 45
Klein G 53
Knebel L 14
Kodama K 121
Kodama T 35
Kohler PF 12
Kojima O 43
Kolaric K 21
Kosaka K 104
Kragballe K 32
Kripke ML 51
Kuang Y 2
Kubonishi S 30
Kuhn C 103
Kumagai K 115
Kung PC 81
Kunicka A 22
Kurashige S 121
Kuruvilla A 37
Lacko E 120
Lalague ED 19
Lang I 108
Larsson EL 125
Leary PL 96
Lee GD 83
Lee LF 64
Lester EP 80
Levin MJ 96
Levin RH 85
Li C 2
Li J 3
Liao Y 3
Lin HS 103
Lindemalm C 10
Lindner A 13
London J 80
Longmire J 47
Lospalluti M 25
Lozzio BB 8
Lublin DM 88
Lukas A 41
Lukas W 41
Mackay IR 113
Mackay IR 16
Mackay IR 39
Madgar I 13
Madon E 33
Magrath IT 71
Majima S 43
Mak TW 116
Malenica B 21
Malesky EV 12
Many M 13
Maricic Z 21
Mashiba H 97
Massner B 14
Masucci MG 45
Masuda T 87
Matheson DS 79
Mathews HL 102
Matsuda M 44
Matsunaga K 97
Matysiak M 17
Mayer P 101
McCarthy KF 56
McCarthy WH 124
McCulloch EA 116
McKenzie IF 66
McMaster BE 119
Mellstedt H 10
Mellstedt H 26
Mellstedt H 9
Meneghini CL 25
Merino F 55
Merrili J 67
Meshulam DH 69
Michaelides M 66
Mikata A 44
Mikata A 44
Milas L 21
Miller G 133
Minato K 135
Minden MD 116
Minowada J 69
Mitchell MS 122
Mitsuhashi S 121
Mitsui T 128
Miwa T 104
Mohri M 44
Montella F 5
Morgat JL 136
Mori KJ 114
Mori KJ 115
Mori M 104
Mori S 44
Moroz C 13
Muller JM 94
Murray E 124
Mustill BM 64
Naha PM 89
Namba K 44
Nawata J 35
Nekam K 108
Newborg MF 98
Newecka-Samol T 18
Newecka-Samol T 40
Nielsen JL 32
Niitani H 100
Niiya K 30
Nikolowski J 24
Nishimura H 35
Nishioka B 43
Nishioka K 84
Nishioka M 35
Nola P 21
Nomura Y 97
North RJ 98
Nowak HF 95
Nowakowska K 22
Nowell PC 130
Noyes RD 84
Ochocka M 18
Ochocka M 40
Oh A 43
Ohmura T 30
Ohsawa N 104
Opolski A 127
Oshimura M 104
Osipov SG 6
Out TA 117
Ozaki A 100
Pajdak E 99
Pan J 3
Parente R 1
Pastore G 33
Payne CM 134
Pelletier L 19
Perek D 22
Perry L 81
Perry S 59
Petranyi J 11
Petrini B 23
Pettersson D 26
Pettersson D 9
Phillips JH 84
Pichlmaier H 94
Pierson G 131
Pieskus J 110
Pilkington GR 112
Pituch-Noworols 99
Pleau JM 136
Powell JM 59
Powell PC 64
Pregowski W 95
Priestman TJ 82
Purtilo D 45
Rabson M 133
Radley JM 50
Rao VS 122
Rataan Y 36
Reischl G 11
Rennie M 64
Richardson CR 90
Riglar C 16
Rocklin RE 69
Rogan-Grgas J 21
Ronchese F 73

Rosenberg JS 62
Rosendaal M 91
Rossiter H 101
Rumiantsev AG 6
Rumke HC 117
Russell IS 39
Russo AJ 76
Sadauskas P 110
Saha NK 37
Saijo N 100
Sasaki A 136
Sato N 104
Saxena QB 58
Saxena RK 58
Schat KA 65
Schirrmacher V 52
Schmoeckel C 24
Schocket AL 12
Schreiber H 51
Scriba M 101
Servadei F 1
Seto A 115
Shek WR 65
Shiku H 129
Shimoyama M 135
Shiomi F 30
Shiraishi M 57
Shiraishi Y 30
Siwinska-Golebi 22
Skinner GR 34
Skoog L 53
Smith CI 9
Smith SR 86
Smith Y 86
Smogorzewska E 22
Soderling CC 49
Sokolowski K 46
Solling J 32
Somers R 7
Sonta-Jakimczyk 41
Sroczynska M 41
Stavrou D 63
Stevens SK 118
Stewart CC 105
Stosiek U 14
Strzadala L 127
Stunkel K 24
Suchi T 44
Summerfield GP 31
Sun Y 2
Surovas V 110
Szigeti R 45
Taguchi H 30
Takagi K 44
Takemoto T 35
Tamosiunas V 110
Tan YH 79
Tennican PM 134
Terasaki P 126
Terminelli C 86
Terpstra FG 117
Testa D 81
Thoman ML 72
Thomasson DL 105
Thyresson N 23
Tojima K 44
Tomida M 38
Torok K 108
Tosato G 71
Trepel J 80
Trepinska E 46
Tsang KY 48
Turner SP 34
Twig S 13
Ueda N 30
Uehara Y 43
Ueymama Y 104
Ullberg M 67
Urban JL 51
Vallera DA 49
Van Beek WP 7
Van Damme J 78
Van Soesbergen 7
Vanky F 20
Vena GA 25
Vermylen C 78
Voci MC 5
Von Stedingk LV 23
Vonderheid EC 130
Wade MJ 70
Wakasa A 44
Waldman SR 15
Warner NL 109
Wasserman J 23
Watanabe S 44
Watson DB 113
Weigle WO 72
Weiss JF 56
Weissman IL 118
Wessel-Aas T 29
Wildgoose J 90
Wong BL 69
Wust CJ 8
Yagawa K 97
Yamada K 129
Yamaguchi H 129
Yamamoto Y 38
Yefenof E 111
Yen SE 105
Yodoi J 87
Yonemoto RH 15
Yong WK 77
Yoshinaga H 97
Yunis EJ 93
Yust I 36
Zanovello P 73
Zardawi IM 37
Zeijlemaker WP 117
Zhang G 2
Zimnoch L 95
Zuberi RI 74

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In this issue:

- **EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS.................. 1-65**
- **EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS................................ 66-97**
- **EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION.. 98-142**
- **THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE.. 143-162**
- **ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY................................ 163-164**
- **RELATED BIOLOGY OF IMMUNE CELLS.. 165-181**
- **CMI METHODOLOGY................................... 182-186**
- **SUPPRESSOR CELL ACTIVITY.................. 187-193**
- **OTHER RELATED STUDIES....................... 194-203**

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HE 20. 3173/2:

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. AMYL NITRITE MAY ALTER T LYMPHOCYTES IN HOMOSEXUAL MEN.

Goedert JJ, Wallen WC, Mann DL, Strong DM, Neuland CY, Greene MH, Murray C, Fraumeni JF, Blattner WA
Environmental Epidemiology Branch, NCI, Landow Building - Room 4C18, Bethesda, MD, 20205
Lancet; 1(8269):412-416 1982

To evaluate the recent outbreak of Kaposi's sarcoma (KS) and opportunistic infections in homosexual men, clinical, virological, and immunological data on 2 homosexual men with KS and on 15 healthy homosexual volunteers were collected. Both KS patients had regularly used amyl nitrite or butyl nitrite (AN); they had low helper/suppressor (H/S) T lymphocyte ratios before chemotherapy and high titers of antibody against cytomegalovirus (CMV). Eight of the 15 volunteers were regular AN users; 7 of the 8 had low H/S ratios due to larger than normal numbers of OKT8-positive suppressor cells and smaller numbers of OKT4-positive helper cells. In all eight AN users the fluorescence profile obtained with monoclonal antibody 9.6 (which detects the sheep E-rosette receptor) was bimodal, indicating a subpopulation of T cells with increased receptor density. A similar pattern was observed when OKT8, the antibody which detects cytotoxic suppressor cells, was used. Two of the seven men who did not use AN had abnormal fluorescence with reagent 9.6, and one of these also had a low H/S ratio. CMV-antibody titers were persistently high in 14 of the 15 healthy men, but the titers were not related to AN use or T-cell abnormalities. The data suggest that nitrites may be immunosuppressive in the setting of repeated viral antigenic stimulation and may contribute to the high frequency of KS and opportunistic infections in homosexual men. (Author abstract) (35 Refs)

2. CLINICAL ASSESSMENT OF PATIENTS WITH HEAD AND NECK CANCERS USING HEMATOLOGICAL, SEROLOGICAL, AND IMMUNOLOGICAL PARAMETERS.

Okamoto M
Dept. Otorhinolaryngology, Kitasato Univ. Sch. Medicine, Kanagawa 228, Japan
Nippon Jibiinkoka Gakkai Kaiho; 84(11):1408-1423 1981

Hematological, serological, and immunological parameters were assessed in 121 patients (92 men, 29 women) who had squamous cell carcinoma of the head and neck region and who were treated with either surgery or radiotherapy. Sites of cancers included the upper jaw in 29 of the patients, larynx in 45, upper pharynx in 18, middle pharynx in 5, cheek in 4, and others in 20. Peripheral blood lymphocyte count, T-cell count, and phytohemagglutinin blast-formation rate were used as parameters of cellular immunity. Serum immunoglobulins, complement components C3 and C4, CH50, carcinoembryonic antigen, and alpha-1-antitrypsin were used as parameters of humoral factors. Prior to treatment, the patients with pharyngeal cancer, advanced cancer, or poor prognosis frequently showed subnormal cellular immunity. Decreases in markers of cellular immunity varied according to treatment; marked decreases following treatment were observed particularly in patients with pharyngeal, upper jaw, or advanced cancer. The decreased cellular immunity following treatment improved rapidly after surgery but more slowly after radiotherapy. Hematological, serological, and immunological parameters must be considered along with appearance and functional preservation when treatment is being chosen for patients with head and neck cancers. **(42 Refs) (In JPN)**

3. B CELL, HELPER T CELL, AND SUPPRESSOR T CELL ABNORMALITIES CONTRIBUTE TO DISORDERED IMMUNOGLOBULIN SYNTHESIS IN PATIENTS FOLLOWING BONE MARROW TRANSPLANTATION.

Korsmeyer SJ, Elfenbein GJ, Goldman CK, Marshall SL, Santos GW, Waldmann TA
Metabolism Branch, NCI, NIH, Bethesda, MD, 20205
Transplantation; 33(2):184-190 1982

The pathogenic mechanisms responsible for the hypogammaglobulinemia that occurs in patients who have undergone bone marrow transplantation were studied using peripheral blood lymphocytes in an in vitro immunoglobulin biosynthesis assay. None of the nine marrow recipients between 2 and 15 mo after transplantation produced normal amounts of IgG, IgA, or IgM in response to pokeweed mitogen (a T cell-dependent activator). However three of these same patients responded to Epstein-Barr virus (a helper T cell-independent activator), suggesting that these possessed responsive B cells. Cocultures of the marrow recipients' lymphocytes with lymphocytes from their respective donors or other normal subjects documented excessive suppressor cell activity in five cases. These suppressor cells frequently had profound activity (greater than 80% suppression of the immunoglobulin synthesis of cocultured normal cells), were predominantly radioresistant, and were T cells in the cases where analyzed. Helper T cell activity for immunoglobulin synthesis was not demonstrable in seven of the nine cases. In addition, four of the patients apparently possessed defective B cells. Although most patients had combined defects of several lymphocyte subpopulations, it appeared that either an isolated helper T cell or isolated B cell deficiency was sufficient to result in altered Ig synthesis. In this regard, two patients had demonstrable helper T cell defects with partially responsive B cells and no excessive suppressor activity. Interestingly, these two patients were experiencing a recurrence of their hypogammaglobulinemia following a period of normalized immunoglobulin levels. Thus, defects within all lymphocytic elements involved in the response and regulation of immunoglobulin synthesis were identified and may contribute to the humoral immunodeficiency which follows marrow transplantation. (Author abstract) (25 Refs)

4. ANALYSIS OF NATURAL KILLER ACTIVITY AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH PRIMARY LUNG CANCER AND METASTATIC PULMONARY TUMORS.

Saijo N, Shimizu E, Irimajiri N, Ozaki A, Kimura K, Takizawa T, Niitani H
Dept. Internal Medicine, Natl. Cancer Center Hosp., Tsukiji 5-1-1, Chuo-Ku, Tokyo 104, Japan
J Cancer Res Clin Oncol; 102(3):195-214 1982

To clarify the contribution of ADCC and NK activities to host immune response against cancer, the characteristics of cells mediating these activities were examined in the peripheral blood lymphocytes of normal volunteers, and the changes of these activities were also evaluated in patients with lung cancer and metastatic pulmonary tumors before and after chemotherapy. OAT cells derived from small cell carcinoma of the lung and K-562 cells derived from erythroleukemia were used as target cells of ADCC and/or NK assay. ADCC and NK activities were not changed according to age, sex, and blood type. Mild and marked personal differences were observed in ADCC and NK activity, respectively. These activities were also influenced by environment. ADCC and NK activities of normal adult volunteers were diversely correlated at the coefficient of gamma-0.426. NK activities were high against K-562 and CCRF-CEM cells, and low against BALL and OAT cells. NK activity against K-562 cells was strongly inhibited by K-562 or CCRF-CEM cells with high NK sensitivity, on the other hand, it was slightly inhibited by OAT and BALL cells with low NK sensitivity. NK activity against OAT cells was strongly inhibited by OAT, K-562 and CCRF-CEM cells, but not inhibited by BALL cells. The effector cells mediating NK activity were identified as non-adherent, E-receptor-positive, Fc-receptor-positive small lymphocytes. NK activity was not decreased before chemotherapy in patients with stage III primary lung cancer and metastatic pulmonary tumors. It was decreased only in patients of bad performance status, and it was significantly decreased in all patients after chemotherapy. ADCC also exhibited the tendency to decrease after chemotherapy in tumor-bearing patients. The recovery of NK-activity after chemotherapy well correlated with the effect of chemotherapy. (Author abstract) (53 Refs)

5. ROLE OF AUTOLOGOUS LYMPHOCYTE CYTOTOXICITY IN COLONIC NEOPLASIA.

Gallagher P, Vose BM, Moore M, Schofield PF
Teaching Unit 5, Withington Hosp., West Didsbury, Manchester 20, England
Gut; 23(1):31-35 1982

The T-lymphocyte mediated killing of autologous carcinoma colon cells was investigated. There was no change in the incidence of activity with advanced disease, age, or nutritional status of the patient and no difference could be demonstrated in lymphocytes extracted from blood, draining lymph nodes, or the tumor itself. Nevertheless, T-lymphocyte activity did appear to be specific for the patient's own tumor, as it was rarely observed with allogeneic tumors. There was also no correlation with lymphocyte natural killer activity. The in vitro studies demonstrated patient specific T-lymphocyte activity in 23 of 47 patients with carcinoma of the colon, but the results do not correlate with clinical and pathological findings. (Author abstract) (15 Refs)

6. DEVELOPMENT OF RISK FACTOR PROFILES FOR INDIVIDUALS WITH INCREASED SUSCEPTIBILIT Y TO CANCER OF THE LARGE INTESTINE.

Lipkin M, Nordlicht N, Nigro ND, Wogan GN, Montesano R, Venitt S, Bruce WR, Archer MC, Wilkins TD
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Banbury Rep; 7:97-118 1981

Several populations at high risk of colorectal cancer (CRC) have been registered at Memorial Hospital, including asymptomatic persons and spouses: hereditary polyposis syndromes; site-specific CRC without polyposis; familial multiple cancers inducing CRC; and CRC patients with a second primary malignancy and a family history of CRC, cancer other than CRC, or no cancer. The registry also includes data on families having 41 cancer-free members over at least two generations. In familial CRC, the age at CRC onset differs significantly from the age at CRC onset in the general population. An attempt is being made to identify persons at high risk of CRC who are destined to develop CRC. The phenotypic characteristics collected into the 'risk profile' for patients with familial polyposis include the percentage of 3H-thymidine-labeled epithelial cells in the upper third of the colonic crypts in random biopsy specimens of flat colonic mucosa; the carcinoembryonic antigen content of colonic lavage specimens; mixed lymphocyte reactivity to allogeneic stimuli; the distribution of normal and abnormal actin concentrations in cultured cutaneous fibroblasts; and fecal concentrations of undegraded cholesterol and 7-alpha-dehydroxylase. A systematic analysis of the effects of stress on these parameters has also been started. Other risk factor profiles for other CRC risk groups are being formulated. (39 Refs)

7. SPECIFIC AND NON-SPECIFIC LYMPHOCYTE CYTOTOXICITY IN COLON CARCINOMA.

Vose BM, Gallagher P, Moore M, Schofield PF
Dept. Immunology, Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, Eng
Br J Cancer; 44(6):846-855 1981

The cytotoxic activity of peripheral-blood (PBL), lymphnode (LNC) and tumor-infiltrating lymphocytes (TIL) from 47 patients undergoing surgery for colon carcinoma (Duke's Stage A, 1 patients; B, 24; C, 15 and C with metastases, 7) was examined in short-term 51Cr-release assays, against fresh autologous tumor cells, allogeneic colon cancer cells and the erythroleukemia cell line, K562. Cytotoxicity against autologous cells was detected in at least one effector population in 23/47 patients (49%), with overall frequencies which did not differ for patients in different Duke's stages of disease. By contrast, lysis of allogeneic tumor cells was infrequent (11%) regardless of the effector population to which they were exposed. Cytotoxicity against K562, cells highly sensitive to NK activity, though variable, was detected in 93% of PBL of normal donors and 83% of patients, and among the latter showed no evidence of significant decline with advancing disease. However, LNC and TIL anti-K562 activity was infrequent (17%) in concordance with previous reports. There was no correlation between the ability of patients' PBL to lyse autologous tumor and K562 cells. The independence of these two cytotoxic actions was further explored in studies fractionating lymphocytes: autologous tumor killing was augmented in T-enriched PBL; whereas the greatest anti-K562 activity was found in the corresponding non-T fraction. Lymphocyte cytotoxicity in colonic neoplasia is thus manifest in two apparently independent lymphocyte populations; a relatively specific killer T-cell population, detectable in PBL, LNC and TIL, which is preferentially reactive with the autologous cells; and a non-specific killer population, largely limited to PBL, with the properties of NK cells. The activity of neither population reflects the clinical status of patients with this disease. (Author abstract) (28 Refs)

8. HISTOPATHOLOGIC AND HISTOENZYMATIC OBSERVATIONS IN CARCINOMAS TREATED WITH HUMAN LEUKOCYTE INTERFERON.

Knezevic M, Knezevic-Krivak S, Ikic D, Maricic Z, Krusic J, Padovan I, Nola P, Brodarec I, Jusic D, Soos E
Dept. Pathology, 'Dr. Mladen Stojanovic' Univ. Hosp., Vincopracliba 29, 41000 Zagreb, Yugoslavia
Int J Clin Pharmacol Ther Toxicol; 20(1):27-38 1982

Histologic and histochemical examination of the bioptic material of 34 cases of uterocervical carcinoma (UCC) and 30 cases of head and neck tumors treated with crude human leukocyte interferon (HLI) revealed excellent positive response for both types of disease. The UCC patients showed a positive response to therapy in 70% of the cases. The principal reason for nonresponse was evidently failure of interferon to penetrate deeply through the mucosa into extensive tumor growths. HLI significantly enhanced the spontaneous peritumoral defense of tissue in cases of carcinoma microinvasivum and carcinoma in situ. In the cases of carcinoma of the skin, lips, and oral cavity, interferon definitely had a positive effect in 80%, a healing effect in 50%, and a very likely healing effect in an additional

25%. HLI stimulated the infiltration of stroma with the masses of lymphocytes and macrophages. Macrophages showed signs of increased activity, and new lymph nodules were observed at the site of the tumor. (22 Refs)

9. AN IMMUNOLOGICAL ASSESSMENT IN PATIENTS WITH UTERINE CERVIX CARCINOMA.

Bonneterre J, Santoro F, Wattre P, Beuscart R, Adenis L, Capron A
Centre Oscar-Lambret, rue Frederic-Combemale, B.P. 307, F 59020 Lille, France
Gynecologie; 32(3):257-266 1981

The relationship between cellular and humoral immunity parameters and stage, treatment and prognosis of cervix cancer was examined in 111 women with carcinoma in situ (12: mean 48.2), Stage I or II neoplasms (57: mean age 52.2), or Stage III or IV neoplasms (42: mean age 62.4). Increased inhibition of phytohemagglutinin (PHA)- or concanavalin A-induced lymphoblastic transformation was evident in more advanced cancers. The percentage and absolute number of T-lymphocytes was identical in the three groups. The percentage of B-lymphocytes was increased in more advanced cancers while the absolute number of B-lymphocytes remained constant. Tuberculin skin tests were positive in 3/7 patients in Group I, 12/32 in Group II, and 8/12 in Group III. Thirty-eight of 93 patients had abnormal levels of circulating immune complexes. The mean plasma carcinoembryonic antigen levels were 8.4, 12.9 and 48.9 nanog/ml for Groups I, II, and III, respectively. No significant difference in IgG and IgM concentrations were observed as a function of group. The mean level of IgA was significantly increased in Group III patients. Complement 3 activity increased with more advanced cancers; complement 4 activity was increased in Group III patients. Various analysis found some associations between clinical and immunological parameters: age of patients, complement factors, and circulating immune complexes; lymphoblastic transformation with mitogens also were closely correlated. Linear regression test demonstrated a relationship between lymphoblastic transformation and skin tests and circulating immune complexes and levels of carcinoembryonic antigen, IgA, IgM, and complement 3. (58 Refs) (In FRE)

10. LEUKOCYTE MIGRATION INHIBITION ASSAY IN PATIENTS WITH PROSTATE ADENOCARCINOMA.

Wright GL, Schellhammer PF, Reid JW, Seig SM, Faulconer RJ, Brassil DN
Dept. Microbiology and Immunology, Eastern Virginia Medical Sch., P.O. Box 1980, Norfolk, VA, 23501
Prostate; 2(2):121-131 1981

The leukocyte migration inhibition (LMI) assay was used to measure cell-mediated immunity (CMI) responses in 44 patients (56-92 yr old) with prostate cancer as a measurement of putative tumor antigens in 3 M KCl extracts of fresh tumor tissue. Six patients had Stage A disease, 12 Stage B, 11 Stage C, and 15 Stage D. Controls included 13 patients with transitional cell carcinoma of the bladder, 18 with renal cell carcinoma, 14 with breast carcinoma, 4 with colon carcinoma, 4 with lung carcinoma, 19 with benign prostate hyperplasia, and 30 normal volunteers. Using a prostate tumor extract, LMI was found in 27/44 (61%) of patients with prostate tumors, 7/19 (37%) with benign prostatic hyperplasia, 26% of patients with nonprostatic cancers, and 10% of normal donors. Control extracts obtained from normal prostate tissue, benign prostate hyperplasia tissue, and tissues from other tumors had statistically less LMI reactivity when reacted against WBC from patients with prostatic tumors. LMI reactivity of prostate cancer patients did not correlate with the clinical state of disease, although there was less reactivity with advanced disease. (21 Refs)

11. THE USE OF ESTRAMUSTINE PHOSPHATE (ESTRACYT) IN THE CONTROL OF PROSTATIC CANCER.

Sadi A, Garrone GO, Saad FA
Disciplina de Urologia, Escola Paulista de Medicina, Rua Botucatu, 840 - Vila Clementino, 04023 - Sao Paulo - SP, Brazil
Folha Med; 83(Suppl2):516-520 1981

Twenty-one men (57-84 yr old) with prostatic carcinoma (PC) in Stage B2 (6), Stage C (1), or Stage D (14) were treated with estramustine phosphate (EP: 140 mg/tablet) in doses from one tablet every other day to four tablets/day. Regular follow-up examinations were performed via hemograms, analyses of phosphatases (alkaline, acid, and prostatic acid), glycemia, bilirubin, urea, creatinine, lymphocytes T and B, and excretory urography and osseous scintigraphy. The patients tolerated EP well; only four had nausea at the beginning of treatment for a short period of time. Urination improved in 10 patients. Eleven of the patients never had pain, and of the 10 patients who had lumbar pain or pain in the limbs at the beginning of treatment, 8 were asymptomatic 3 wk later. Three patients with sexual function at the beginning of treatment maintained function. Results of most tests including those for B lymphocytes remained in the normal range. T lymphocyte levels were reduced in 50% of patients. In some cases the dosage of EP was reduced to 1/3 or 1/4 with favorable response maintained in many. (13 Refs) (In POR)

12. METABOLIC IMMUNODEPRESSION AND METABOLIC IMMUNOTHERAPY. AN ATTEMPT OF IMPROVEMENT IN IMMUNOLOGIC RESPONSE IN BREAST CANCER PATIENTS BY CORRECTION OF METABOLIC DISTURBANCES.

Dilman VM, Berstein LM, Ostroumova MN, Fedorov SN, Poroshina TE, Tsyrlina EV, Buslaeva VP, Semiglazov VF, Seleznev IK, Bobrov YF, Vasilyeva IA, Kondratjev VB, Nemirovsky VS, Nikiforov YF
N. N. Petrov Res. Inst. Oncology, 68, Leningradskya St., Pesochny-2, Leningrad 18846, USSR
Oncology; 39(1):13-19 1982

The effects of administration of phenformin and clofibrate to 32 breast cancer patients who underwent radical mastectomy and suffered from hormonal metabolic disturbances involving a decline in immunologic response were investigated. It was demonstrated that treatment with these drugs during 2-7 mo results in an improvement in metabolic parameters and delayed hypersensitivity reaction to DNCB, tuberculin and candidin (75.5% of cases), an increase in T lymphocyte count (56.3%) and an improvement of the reaction of lymphocyte blast transformation (66.6%). The improvement in the immunologic status of the patients persisted for 6-8 wk after the stoppage of phenformin administration; a gradual decline in immunologic response and return to the original level were recorded 4-6 mo after stoppage of phenformin therapy. The effect of clofibrate on metabolic and immunologic parameters did not manifest itself as soon as 6-8 wk after stoppage. Elimination of metabolic immunodepression, which gradually develops in the course of normal aging and tumor process, should be the main objective of metabolic immunotherapy. To this end, therapeutic means, other than phenformin and clofibrate, may be used provided they exert the same effects on carbohydrate-fat metabolism. The desirability of study of the effects of a long-term course of drugs of this kind on the therapy of cancer patients is discussed. (Author abstract) (35 Refs)

13. PATIENTS' IMMUNE RESPONSE TO BREAST AND LUNG SPECIFICITY.

Springer GF, Murthy SM, Desai PR, Fry WA, Tegtmeyer H, Scanlon EF
Immunochemistry Res., Evanston Hosp., 2650 Ridge Ave., Evanston, IL, 60201
Klin Wochenschr; 60(3):121-131 1982

We report here sensitive and specific measurement of immune responses of patients with certain kinds of carcinoma toward the physically and chemically well defined T antigen isolated from healthy human erythrocytes. Over 90% of adenocarcinoma tissues tested possess T-specific immunoreactive structures as determined with human antisera, in contrast to healthy tissues and benign lesions. Adenocarcinoma patients recognize the carcinoma-associated T antigen as foreign. Delayed-type skin hypersensitivity reaction to T antigen (DTHR-T) was tested. In vitro leukocyte migration inhibition and scoring of anti-T hemagglutinin titer using the T-anti-T system diagnosed many adenocarcinomata correctly, but these tests were generally less sensitive and specific than the DTHR-T. This system may also be of screening and monitoring value. Surgical removal of primary carcinoma led to a rebound of anti-T in breast carcinoma patients and its renewed decrease in some, prior to clinical recurrence of cancer. Also, the DTHR-T turned from positive to negative in some Stages I and II breast and T1-2 N0-1 M0 lung adenocarcinoma patients who had no demonstrable relapse during the ensuing observation period. (75 Refs)

14. IMMUNOLOGIC STATE OF PATIENTS WITH OPERABLE MAMMARY CANCER.

Hrsak KM, Rudolf M, Kubovic M, Martinac P, Bulic N, Katelan M
Zavod za klinicku onkologiju i radioterapiju, Klinicki bolnicki centar, Rebro, Zagreb, Yugoslavia
Libri Oncol; 10(2/3):323-326 1981

Immunologic state was evaluated in 44 healthy controls (HC) and in 49 patients with operable mammary cancer (MC) in different stages of the disease with the aid of mitogens reactivity [phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM)], T and B lymphocytes, and the most active T lymphocytes (E, M, and A rosettes) in peripheral blood. Patients were tested before receiving any therapy. Reactivity to mitogens was lower in MC compared with HC patients. Most pronounced reactivity was seen when tested with PHA. Difference in reactivity between Stage I and the other two could be observed. Total number of T and B lymphocytes was reduced, but that reduction was less significant than the reactivity to mitogens. Most active T lymphocytes were higher in Stage II patients with MC than in HC. (8 Refs) (In SCR)

15. ADJUVANT RADIATION THERAPY COMPARED WITH CYCLIC CHEMOTHERAPY IN PATIENTS WITH MAMMARY CARCINOMA. II. CHANGES OF MITOGEN RESPONSES OF BLOOD LYMPHOCYTES.

Strender LE, Blomgren H, Wasserman J, Petrini B, Baral E
Radiumhemmet, Karolinska Sjukhuset, S-104 01 Stockholm, Sweden
Acta Radiol Oncol Radiat Phys Biol; 20(5):299-304 1981

Blood lymphocyte reactivity to purified protein derivative of tuberculin (PPD) and phytohemagglutinin (PHA) was examined in 62 patients with breast carcinoma who received postoperative adjuvant radiation therapy or cyclic chemotherapy with chlorambucil, methotrexate and 5-fluorouracil. Both treatments impaired the immunologic reactivity of blood lymphocytes as measured by PPD and PHA stimulation in vitro. Radiation therapy seemed to cause more profound and protracted suppression of the PPD response than chemotherapy. (Author abstract) (20 Refs)

16. MORPHOMETRICAL ANALYSIS OF T- AND B-CELL COMPARTMENTS OF SPLEENS IN HODGKIN'S DISEASE.

Timens W, Koudstaal J, Poppema S
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Virchows Arch [Cell Pathol]; 38(3):291-296 1982

One possible explanation for the defective cellular immunity in Hodgkin's disease is an abnormal distribution of T lymphocytes. To study this possibility a morphometric analysis of T- and B-areas in non involved and involved spleens of patients with Hodgkin's disease was undertaken. We found that in involved spleens a significant reduction of the T dependent area could be demonstrated. We concluded that this reduction is caused by an abnormal distribution of T lymphocytes in the spleen and may partly explain the defects in cellular immunity. In addition, the absence of overlap between the T/B area ratios of involved and non-involved spleens suggests, that a prediction on involvement of spleen can be made by morphometrical analysis of a small, random taken non-involved area. (Author abstract) (13 Refs)

17. IMPAIRED AUTOLOGOUS MIXED LYMPHOCYTE REACTIVITY IN HODGKIN'S DISEASE.

Begemann M, Claas G, Falke H
Med. Univ.-Klinik, Emil-Mannkopff-Str. 1, D-3550 Marburg, W. Germany
Klin Wochenschr; 60(1):19-26 1982

In patients with Hodgkin's disease, the impaired immune reactivity, especially of the thymus dependent system, is well established. The decreased immune response of the lymphocytes from the peripheral blood contrasts to an increased lymphocytopoiesis in the lymphatic organs with a hyperplasia of these tissues. We studied the reactivity of peripheral T lymphocytes from 20 patients with Hodgkin 's disease and 26 healthy control persons against autologous and allogeneic non T cells respectively in the mixed lymphocyte culture (MLC). Our experiments show an extremely depressed autologous mixed lymphocyte reactivity (MLR) of T lymphocytes from patients with Hodgkin's disease compared to those from normal donors. In the allogeneic MLC, the proliferation of the patients' T cells was stronger than in the autologous MLC, but significantly lower than the proliferation of normal T lymphocytes when stimulated by normal non T cells. Patients' non T cells stimulated T lymphocytes from healthy donors as well as non T lymphocytes from normals did. Finally, the autologous MLR of normal lymphocytes was significantly suppressed by 18 of 23 sera from Hodgkin's patients when these sera were substituted for normal AB serum in the cultures. These results demonstrate an impaired function of T lymphocytes from patients with Hodgkin's disease in the autologous MLC and the presence of one or more factors in their serum which inhibit the proliferation of normal lymphocytes in the autologous MLC. The role of suppressor cells and their factors will be discussed. (Author abstract) (65 Refs)

18. ULTRASTRUCTURAL COMPARISON OF HODGKIN'S AND NON-HODGKIN'S LYMPHOMAS.

Peiper SC, Kahn LB
Dept. Pathology, St. Jude Children's Res. Hosp., 332 North Lauderdale, P. O. Box 318, Memphis, Tennessee, 38101
Histopathology; 6(1):93-109 1982

Ultrastructural features of Reed-Sternberg (RS) cells were compared with those of neoplastic large lymphoid cells from a variety of non-Hodgkin's lymphomas of large cell type (large cleaved and non-cleaved follicle center cells, immunoblasts, lymphoblasts) and with those of non-neoplastic macrophages, including epithelioid cells present in the lesions. The RS cell cytosol contained an abundance of organelles, frequently in a dense paranuclear location. The Golgi apparatus was hyperplastic and multiple, and glycogen and lipid droplets were frequently demonstrated in the same cell. The large lymphocytes of follicular center cell lymphomas had a sparse, non-complex population of cytoplasmic organelles, the immunoblastic lymphoma had more abundant polysomes and rough endoplasmic reticulum and a well-developed Golgi. The reactive epithelioid histiocytes also had a complex population of cytoplasmic organelles including angulated lysosomes, lipid droplets, tubular mitochondria, and cytoplasmic filopodia. Reactive histiocytes were the cells most likely to be confused with RS cells at the ultrastructural level, especially when the nucleoli were prominent. RS cells bore a closer resemblance to the reactive epithelioid histiocytes than to neoplastic large lymphoid cells. Such a finding favors the non-lymphoid origin of the RS cell. (23 Refs)

19. ACTIVITY OF NATURAL KILLER CELLS IN PATIENTS WITH MALIGNANT MELANOMA.

Masserini C, Villa ML, Rovini D, Clerici E
Cattedra di Immunologia, Universita degli Studi di Milano, Via Venezian, 1, 20133 Milano, Italy
Boll Ist Sieroter Milan; 60(4):307-315 1981

Decreased cytotoxicity of natural killer (NK) cells was observed in patients with malignant melanoma (MM), and the relationship of this decrease to clinical stage of the patients or to suppressive humoral and cellular factors was studied. Of 33 patients (17 men, 16 women; av ages 49 -18 yr and 42 -12 yr, respectively), 8 had primary tumors, 9 had local and regional metastases, and 16 had distant metastases. The study was performed prior to surgery. No chemotherapy was received by the patients. Controls consisted of 43 volunteers of approx the same sex and age. The cytotoxicity was measured by release of Cr. In eight patients, NK cell activity was completely absent. No significant correlation could be noticed between the cytotoxicity of the NK cells and the clinical stage of the patients. (38 Refs) (In ITA)

20. PILOT STUDIES USING MELANOMA TUMOR-ASSOCIATED ANTIGENS (TAA) IN SPECIFIC-ACTIVE IMMUNOCHEMOTHERAPY OF MALIGNANT MELANOMA.

Hollinshead A, Arlen M, Yonemoto R, Cohen M, Tanner K, Kundin WD, Scherrer J
Dept. Medicine, George Washington Univ. Medical Center, 2300 I St., N.W., Washington, DC, 20037
Cancer; 49(7):1387-1404 1982

Highly purified melanoma TAA which induce melanoma-related cell-mediated immune responses have been further characterized using hyperimmune TAA antisera after affinity chromatography for double immunodiffusion-immunoelectrophoresis and indirect immunofluorescence studies. An additional study of antigenic modulation was performed in 23 nonanergic and seven anergic melanoma patients, tested simultaneously with melanoma TAA prepared from primary and metastatic tumors, which had been obtained from one patient at different time periods. The results of pilot clinical trials are reported, including toxicity, timing and dosage studies in 20 patients and subsequent studies of patients with metastatic melanoma treated at three separate centers, using a single lot of purified, allogeneic melanoma TAA. The results of these latter studies in 51 patients with Stage III (distantly metastatic) melanoma and in five patients with earlier stages of disease indicate that: (1) when the interval from primary therapy to recurrence is greater than 1 yr and when liver, bone and brain are not involved, partial or total clinical regression may be noted in up to 25% of patients with metastatic disease receiving immunochemotherapy; (2) when total regression does occur, the effect usually lasts from 1 to 3 yr; (3) cytoreductive (debulking) surgery, when possible, in cutaneous, nodal retroperitoneal, and visceral regions may enhance the response to specific active immunochemotherapy, although some debulked patients had less tumor burden, and t his factor alone may lead to an improved prognosis in patients undergoing any subsequently treatment; (4) when circulating inhibitory factors are modified through preimmunization chemotherapy, an enhanced host response may be seen; and (5) Cancer Serum Indices (CSI) may be useful in predicting recurrence and in following tumor load and response to therapy. Information obtained from these studies suggests the need for further trials to determine the effect of immunization on patients with earlier stages of disease where recurrence rates remain high, and to evaluate the mechanisms of tumor rejection or tumor progression in the face of immune stimulation. (Author abstract) (32 Refs)

21. AN ULTRASTRUCTURAL STUDY OF THE MONONUCLEAR CELL INFILTRATE OF MYCOSIS FUNGOIDES AND POIKILODERMA ATROPHICANS VASCULARE.

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Clin Exp Dermatol; 7(1):11-19 1982

Skin biopsies from patients with pre-mycotic eruptions and plaque and tumid mycosis fungoides (MF) were examined by electron microscopy to assess the value of the presence of abnormal lymphoid cells in early diagnosis of MF. In 21/25 specimens from patients with untreated MF and in all 3 from patients with poikiloderma atrophicans vasculare, mononuclear cells infiltrated the epidermis. In all dermal filtrates examined, abnormal lymphoid cells were conspicuous; the cells possessed irregular nuclear outlines ranging from mild indentation to grossly cerebriform shapes. In the dermis, lymphoid cells comprising 30-60% of the infiltrate were seen in a mixed cellular infiltrate composed of normal mature lymphocytes, histiocytes, mast cells, eosinophils, and occasional polymorphonuclear WBC and plasma cells. Lymphoblasts were identified in dermal infiltrates of two patients with tumid MF. Bizarre histiocytic cells resembling the interdigitating reticulum cell of lymph node T cell areas were observed. In epidermal infiltrate, abnormal lymphoid cells infiltrates singly between keratinocytes and less frequently in groups, forming Pautrier microabscesses. Langerhans cells were observed only in the epidermis, usually isolated but occasionally in contact with lymphoid cells. The diagnostic importance of ultrastructural findings in MF is affirmed. (27 Refs)

22. IMMUNOLOGICAL MONITORING OF PATIENTS AFFECTED BY ANAPLASTIC GLIOMA CONCERNING THE EFFECTS OF SURGERY, RADIO-, AND CHEMOTHERAPY: A PRELIMINARY REPORT.

Servadei F, Parente R, Spagnolli F, Gaist G, Padovani R, Bucci M, Steiner L
Divisione di Neurochirurgia, Ospedale Bellaria, Via Altura 3, Bologna, Italy
Acta Neurochir (Wien); 60(1/2):71-80 1982

The authors studied 24 patients affected by anaplastic gliomas as regards immunology. In all of them the authors evaluated the lymphocyte subpopulation (B and T), firstly by simple lymphocyte count, secondly by studying the rosettes E-total and EAC, thirdly by stimulating the lymphocytes with mitogens phytohemagglutinin-P (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM), and lastly by counting the release of Cr51 in Chang liver cells culture in order to obtain antibody dependent cellular cytotoxicity (ADCC). The parameters were also evaluated after surgery and during conventional radio-chemotherapy with BCNU. Whereas the so-called B-pool seems to be unaffected, the preliminary results show that the T-pool (identified by the E-t rosettes and by responses to PHA, PWM, and ConA) is depressed to a statistically significant degree, if compared with a control group. This depression seems to be related to the tumoral mass, and it is not increased by radio-chemotherapy. In addition, ADCC also seems to be depressed in our glioma patients in comparison with a control group and with a group of bladder cancer patients. (Author abstract) (36 Refs)

23. FOUR RESECTED CASES OF PLEURAL MESOTHELIOMA - THEIR DELAYED HYPERSENSITIVE SKIN TESTS AND CLINICAL COURSE.

Chen KM, Shimizu N, Ogino K, Matsumoto S, Okazaki T, Wada T, Teramoto S
Second Dept. Surgery, Okayama Univ., Medical Sch., Okayama, Japan
Nippon Kyobu Geka Gakkai Zasshi; 29(9):1524-1529 1981

The pleural mesothelioma was classified by diffuse type and localized type. The diffuse type was associated with an ominous prognosis. Recently, the immunity condition was attended with this disease. We experienced four cases of this disease, two cases of diffuse type and two cases of localized type. The preoperative symptoms, delayed hypersensitive skin tests, operative finding and postoperative course were reported. (Author abstract) (14 Refs) (In JPN)

24. PROLIFERATION OF TGAMMA-LYMPHOCYTES IN TWO PATIENTS: CLINICAL FEATURES AND FUNCTIONAL PROPERTIES OF THE PROLIFERATING CELLS.

Schlimok G, Thiel E, Rieber EP, Huhn D, Feucht H, Renner D, Riethmuller G
Krankenhauszweckverband, II. Med. Klinik, Langemarckstr. 11, D-8900 Augsburg, W. Germany
Klin Wochenschr; 60(3):133-142 1982

Two patients suffering from proliferation of Tgamma cells exhibited uncommon clinical features, such as activation of intravascular coagulation after low dose irradiation of the enlarged spleen in one patient and isolated neutropenia in the other patient. While the malignant nature of the disease was doubtless in one patient, cell proliferation in the other patient was more likely reactive. In addition to T cell determinants the proliferating cells expressed a monocytic antigen. They did not suppress B-lymphocyte differentiation into plasma cells. In contrast the proliferating cells, especially in one patient, acted as potent effectors in NK and ADCC using melanoma and MOLT 4 target cells. Erythrophagocytosis by Tgamma cells was seen in one patient. The data suggest that subsets of Tgamma cells are related to the monocytic lineage and that these cells can mediate both NKA and ADCC and partly can develop phagocytic activity. (Author abstract) (49 Refs)

25. MYCOSIS FUNGOIDES. CATCHING A GREAT MASQUERADER.

Price NM
Stanford Univ. Sch. Medicine, Palo Alto, CA
Consultant; 22(3):347-350,354-355,359-360 1982

Symptoms, clinical manifestations, differential diagnosis, and treatment of mycosis fungoides (MF) are described. MF is classified as T-cell lymphoma and primarily affects middle-aged to elderly people. The three phases of classic MF (limited plaque, generalized plaque, and tumor phase) may occur yr apart and progress from one to another imperceptibly. Other clinical manifestations are tumor d'emblee, erythrodermic form, and lymph node and visceral involvement. Disorders that must be differentiated from MF during its early phase include psoriasis, pityriasis rubra pilaris, chronic contact dermatitis (CT), lichen simplex chronicus, chronic eczema, syphilis, tuberculosis, leprosy, and cutaneous lymphomas. With a suspicion of MF the diagnosis has to be confirmed histologically by the presence of atypical lymphocytes within the epidermis. Evaluation of lymph nodes and internal viscera after confirmation of histologic diagnosis is mandatory. Treatment with electron beam shows best results during the plaque phase, and side effects are minor. Most commonly used for topical MF treatment is mechlorethamine applied once a day as a 10-20 mg/ deciliter aqueous solution for at least 3 yr after remission of all clinically apparent lesions. CT developed in 30-70% of patients after such a treatment. Combination of nitrogen mustard with an anhydrous ointment base reduced the incidence of CT to 6%. Administration of psoralens followed by exposure to UV light A has to be repeated indefinitely every 1-2 wk or the lesions may recur. Control of infection is the most important factor when widespread metastases exist. Ulcers should be treated by spot orthovoltage therapy. Total body irradiation and treatment with monoclonal anti-T-cell antibodies are being used in attempts to control disseminated disease. (no Refs)

26. NATURAL KILLER (NK) CELLS AND THEIR POSSIBLE ROLES IN RESISTANCE AGAINST DISEASE.

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Clin Immunol Rev; 1(1):1-65 1981

The characteristics of natural killer (NK) cells and their relation to host resistance to disease are reviewed. Topics discussed include the following: general phenotype of NK cells; expression of markers restricted to NK cells; cell lineage of NK cells; possible relationship of NK cells to T cells, macrophages, or monocytes; interpretation of available evidence regarding lineage of NK cells; possible in vivo roles of NK cells; role of NK cells in resistance against tumor cell lines, primary tumors, microbial infections, and bone marrow transplants; role of NK cells in graft-vs-host disease and in regulation of differentiation of normal hematopoietic or other cells; NK cells as secretory and immunoregulatory cells; clinical correlations of NK cells; and implications of NK cells for immunotherapy. (279 Refs)

27. EFFECTIVE MULTIDRUG, MULTIMODALITY CONSOLIDATION THERAPY OF ADULT ACUTE LYMPHOCYTIC LEUKEMIA: A PRELIMINARY REPORT.

Stein RS, Flexner JM, Collins RD
Vanderbilt Univ. Hosp., A-3311, Nashville, TN, 37232
Cancer; 49(5):846-849 1982

Twelve of 13 adult patients with acute lymphocytic leukemia, acute undifferentiated leukemia, or convoluted T-cell lymphoma (T-cell ALL) who were treated with Adriamycin, vincristine, and prednisone achieved a complete remission. An intensive consolidation regimen was administered. This regimen included Cytosine Arabinoside, L-asparaginase, and multiple courses of CHOP (cyclophosphamide, Adriamycin, vincristine, and prednisone). In addition, cranial irradiation and intrathecal methotrexate were administered. By actuarial estimate, 81% of previously untreated patients who achieved a complete remission will remain in remission for more than 2 yr. (Author abstract) (17 Refs)

28. IN VITRO CELLULAR IMMUNE REACTIVITY OF SOLUBLE ANTIGENS OBTAINED FROM CULTURED LEUKEMIC CELLS IN CHRONIC MYELOID LEUKEMIA.

Khare AG, Advani SH, Gangal SG
(c/o Gangal) Immunology Div., Cancer Res. Inst., Bombay 400 012, India
Indian J Exp Biol; 19(6):524-527 1981

The preparation of potent antigenic substances from leukemia cells by culturing in vitro for various time periods was investigated. Antigens prepared from uncultured cells produced significant inhibition of leukocyte migration in 9/11 tests. Leukemic cells cultured for 24 hr yielded antigens with very high lymphocyte transformation activity in 7/11 tests. Chronic myeloid leukemia leukocyte/lymphocyte samples tested with cells cultured for 48 and 72 hr showed a progressive reduction in the number of positive reactions. Leukemic cell antigens prepared after 24 hr of incubation showed greater activity than antigens prepared from uncultured cells. (16 Refs)

29. STUDIES ON THE ABILITY OF MONOCLONAL ANTIBODIES TO SELECTIVELY MEDIATE COMPLEMENT-DEPENDENT CYTOTOXICITY OF HUMAN MYELOGENOUS LEUKEMIA BLAST CELLS.

Ball ED, Kadushin JM, Schacter B, Fanger MW
Dept. Microbiology, Dartmouth Medical Sch., Hanover, NH, 03755
J Immunol; 128(3):1476-1481 1982

A panel of monoclonal antibodies that bind to leukemic blast cells from patients with acute myelocytic leukemia and chronic myelocytic leukemia in blast crisis was studied for their ability to mediate complement-dependent lysis of a variety of cell populations from patients with leukemia, normal blood cells, and human leukemia cell lines. Several of these monoclonal antibodies were selectively cytotoxic to myeloid leukemia cells (AML-1-99, AML-1-211, AML-2-30, CML-75, CML-115, and CML-150). Although they were all capable of binding to normal cell populations, none of these hybridomas were cytotoxic to normal cells. Three of these antibodies (AML-1-211, CML-75, and CML-150) were cytotoxic to some leukemia cell samples only after dilution of the hybridoma supernatant, ie, they showed a prozone. Binding of these three antibodies as well as another, AML-1-201, as determined in a radioimmunoassay, also showed a prozone. Other monoclonal antibodies are described (AML-2-23 and AML-2-9) that mediate complement-dependent cytotoxicity to myeloid leukemia cells as well as selected normal cell types (monocytes and lymphocytes, respectively). The potential clinical utility of these monoclonal antibodies is considered in the context of recently encountered problems in the use of monoclonal antibodies to mediate leukemia cell lysis in vivo. (Author abstract) (23 Refs)

30. THE ROLES OF LEUKAEMIC AND RESIDUAL NORMAL CELLS IN THE PROLIFERATIVE RESPONSE OF CHRONIC LYMPHOCYTIC LEUKAEMIC LYMPHOCYTES TO MITOGENS.

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Clin Exp Immunol; 47(3):689-696 1982

The proliferative response of lymphocytes from patients with chronic lymphocytic leukemia (CLL) to the polyclonal activators, phytohemagglutinin (PHA) and pokeweed mitogen correlates inversely with the logarithm of the circulating lymphocyte concentration in vivo (p less than 0.001). This suggests that the response is due primarily to residual normal cells in the circulation. In support of this postulate, dilution of normal cells reproduced the effect and also induced a delayed response to PHA, which is found frequently with CLL lymphocytes. A combination of autoradiography and immunofluorescence microscopy identified both B and T cells in the responding population in similar proportions from both normal and CLL donors. These data demonstrate that the 3H-thymidine assay used in most mitogenic studies is not suitable alone for investigating the functional capacity of leukemic lymphocytes in CLL and other diseases involving a gross perturbation of lymphocyte populations. (Author abstract) (19 Refs)

31. MITOGEN-STIMULATED IMMUNOGLOBULIN PRODUCTION BY CHRONIC LYMPHOCYTIC LEUKAEMIC LYMPHOCYTES.

Johnstone AP, Jensenius JC, Millard RE, Hudson L

Dept. Immunology, St. George's Hosp. Medical Sch., London SW17 0RE, England

Clin Exp Immunol; 47(3):697-705 1982

The capacity of B cells from patients with chronic lymphocytic leukemia (CLL) to produce and secrete immunoglobulin following mitogen stimulation was investigated using sensitive radioimmunoassays for mu, gamma, alpha, kappa and lambda immunoglobulin chains. Lymphocytes from 7 of the 11 patients studied secreted immunoglobulin in response to pokeweed mitogen (PWM). IgM was always the major immunoglobulin and in five of the seven responders it was the only class detected; only one type of light chain was observed in most cases. This was in contrast to normal lymphocytes which secreted all classes of immunoglobulin (IgM was invariably the lowest) containing both types of light chain. Lipopolysaccharide induced immunoglobulin secretion in only one of four CLL cases. This was again IgM with only one type of light chain. The assays are therefore most probably measuring a response by the leukemic cells. In most CLL cases, immunoglobulin secretion by the residual normal cells, which proliferate in response to mitogen, was not observed. This inability of the normal lymphocytes to differentiate fully into immunoglobulin secreting cells and the block in switching from IgM production to other classes in the leukemic cells may both be attributable to a defect in the regulatory system of the immune response in CLL patients. (Author abstract) (22 Refs)

32. IMMUNOLOGIC EVALUATION OF LONG-TERM EFFECTS OF CHILDHOOD ALL CHEMOTHERAPY: ANALYSIS OF IN VITRO NK- AND K-CELL ACTIVITIES OF PERIPHERAL BLOOD LYMPHOCYTES.

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Am J Hematol; 12(1):19-27 1982

Twenty-five children with acute lymphoblastic leukemia (ALL) were tested for natural killer (NK) and K-cell activity in vitro using the nonsensitized myeloid/erythroid cell line K562 and the K562 sensitized with rabbit antithymocyte globulin, respectively. The patients consisted of two groups: (1) 13 patients in continuous first remission undergoing maintenance chemotherapy and (2) 12 patients in remission for at least 5 yr in whom chemotherapy had been discontinued at least 6 mo before this study. The first group consistently demonstrated a marked depression in their NK activity and antibody-dependent cell-mediated cytotoxicity (K-cell activity), as compared with normal controls. In contrast, normal levels of cytotoxicity were found in the second group of patients off of all chemotherapy. One patient studied while on chemotherapy and on two occasions following discontinuation of maintenance medications demonstrated that while NK and K-cell activity was depressed during therapy, normal activity returned within days when immunosuppressive therapy was stopped. Thus, present modes of chemotherapy clearly had a profound effect on the in vitro NK and K-cell activity; however, no long-term effect on these functions was noted in our studies. (Author abstract) (22 Refs)

33. HAIRY CELL LEUKEMIA: A CONTROVERSIAL ENIGMA.

Kass L

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Med Times; 110(3):72-76 1982

Clinical features, hematologic manifestations, ultrastructure of the hairy cell, bone marrow examination, pathophysiology, and the role of the spleen in hairy cell leukemia (HCL) are reviewed. HCL is characterized by unusual-appearing lymphoreticular cells with characteristic cytoplasmic excrescences. Symptoms include lassitude, frequent soft-tissue infections, pleural effusions containing hairy cells, and splenomegaly. Patients may have pancytopenia, anemia and leukopenia, leukopenia and thrombocytopenia, or anemia and thrombocytopenia. The typical hairy cell has numerous cytoplasmic excrescences along the cell borders and multiple villi typical of B lymphocytes may be seen. Some hairy cells have ruffles and ridges typical of monocytic cells. Bone marrow evaluation is essential for diagnosis. Origin of the hairy cell is controversial; it cannot be characterized as lymphocytic or monocytic with certainty, although a B lymphocyte derivation is favored. Hematologic abnormalities are thought to result from hypersplenism due to splenomegaly. Splenectomy is treatment of choice for HCL. In patients who show disease progression after splenectomy, single-agent chemotherapy may be helpful; in general, however, chemotherapy is considered deleterious because of untoward complications. (23 Refs)

34. IMMUNODEFICIENCIES AND LYMPHOPROLIFERATIVE DISEASES.

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Istituto di Patologia Speciale Medica e Metodologia Clinica, Universita di Ancona, Ancona, Italy

G Clin Med; 62(9):648-655 1981

Relationship between immunodeficiency and lymphomas was studied in 32 patients with non-Hodgkin's lymphoma (NHL) and in 50 with Hodgkin's lymphoma (HL) before and after induction therapy. Values of lymphocytes, rosette E and surface Ig were determined and compared, according to the old Rappaport classification, before any therapy was given, in 25 patients with lymphocytic lymphoma (LL) and 7 with histiocytic lymphoma (HL). All patients were in Stage III or in Stage IV. The values were 36%, 51%, and 33%, respectively, for LL, and 27%, 49%, and 28%, respectively, for HL . Lymphocytosis, lymphocytes T, and B were measured and compared in 50 patients with HL in relation to histotype, clinical stage and effect of therapy. Immunological defects were potentiated by induction therapy. Alteration in immunity of patients with lymphomas and the increasing incidence of autoimmune disease and additional cancer in these patients were discussed. (40 Refs) (In ITA)

35. BONE MARROW AND BLOOD INVOLVEMENT BY LYMPHOMA IN RELATIONSHIP TO THE LUKES-COLLINS CLASSIFICATION.

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Cancer; 49(5):888-897 1982

The incidence, pattern, extent, and morphology of bone marrow involvement in 176 cases of non-Hodgkin's lymphoma (NHL) were studied in relationship to the Lukes-Collins classification. Ninety percent of the cases were B-cell lymphomas; 10% were T-cell lymphomas. In 53% of cases there was bone marrow involvement by lymphoma at diagnosis. Marrow involvement was most frequently found in the small lymphocyte (B), small cleaved follicular center cell (FCC), and convoluted lymphocyte lymphomas. Frequently, the extent of bone marrow biopsy replacement by lymphoma was less than 30%; the pattern of infiltration was predominantly focal (70%). Cytologic agreement between lymph node and bone marrow specimens was always present in small lymphocyte (B), small noncleaved FCC, convoluted lymphocyte, and lymphoepithelioid cell lymphomas. Cytologic diversity between lymph node and marrow was noted in 20% of small cleaved FCC, 40% (2/5) of large cleaved FCC, and 38% (3/8) of large noncleaved FCC lymphomas. In 79% of all involved cases, both bone marrow biopsy sections and aspirate smears were diagnostic of NHL; only biopsy sections were positive in 18%, and only smears were positive in 3%. The Lukes-Collins classification predicts a high incidence of bone marrow involvement for small lymphocyte (B), small cleaved FCC, and convoluted lymphocyte lymphomas. (Author abstract) (14 Refs)

36. CUTANEOUS T-CELL LYMPHOMA, MULTILOBATED TYPE.

van der Putte SC, Toonstra J, De Weger RA, Van Unnik JA
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Histopathology; 6(1):35-54 1982

Problems related to the distinction and accurate classification of malignant and pseudomalignant lymphoreticular proliferation are demonstrated by three cases. Specimens from three lesions were examined using light microscopy, electron microscopy, cytochemistry, immunohistology, and immunofluorescence. All three cases occurred in elderly men (53, 55, and 53 yr old) with tumorous lesions restricted to one region of the skin and remaining so for a considerable time with a relatively benign course. Histopathologically, in one case the cutaneous infiltrates showed sparing of epidermis and upper dermal zone and demonstrated the peculiar combination of pronounced nuclear lobation and marginal nucleoli. The two other cases were similar but had an even more benign course; histopathologically, a less monotonous infiltrate of cells with less marked nuclear lobation was evident. Cases similar to those reported may have been misinterpreted as lymphoid hyperplasia, malignant B-cell lymphoma, or reticulum cell sarcoma of the skin. The three cases were classified as cutaneous T-cell lymphoma, multilobated type. (57 Refs)

37. THE RELATIONSHIP BETWEEN T LYMPHOCYTE SUBSETS AND IA-LIKE ANTIGEN POSITIVE NONLYMPHOID CELLS IN EARLY STAGES OF CUTANEOUS T CELL LYMPHOMA.

Thomas JA, Janossy G, Path MR, Graham-Brown RA, Kung PC, Goldstein G
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J Invest Dermatol; 78(2):169-176 1982

Immunofluorescence studies were carried out in cutaneous T cell lymphoma (mycosis fungoides) in order to analyze the microanatomical relationship of the different T lymphocyte subsets (inducer and suppressor/cytotoxic cell populations) to large nonlymphoid Langerhans-type and so-called 'indeterminate' or interdigitating cells. The conventional and mouse (monoclonal) antibodies were used in various combinations using fluorescein and rhodamine labeled second layers. In five of the seven cases studied the dermal infiltrate consisted of numerous T (HuTLA) lymphocytes, 80-90% of which expressed the inducer phenotype (HuTLA,OKT4). Most of these cells formed close contact with large cells exhibiting large amounts of Ia-like antigens. These cells corresponded to the interdigitating and indeterminate cells in the sections. By contrast, only small numbers (10-20%) of T cells of suppressor/cytotoxic type (HuTLA,OKT8) were seen. These did not show a close affinity to the Ia-like antigen positive nonlymphoid component but appeared to have a predilection for the epidermis. Epidermal Langerhans cells, also strongly Ia-like antigen positive, were further defined by two monoclonal antibodies reacting with a cortical thymocyte antigen HTA-1. Although Langerhans cells are probably related to the Ia-like antigen positive dermal cells only a few of the abundant latter population were HTA-1. In the remaining two cases, larger populations of OKT8 (suppressor/cytotoxic) cells were seen and could be heralding a particularly benign course. These observations indicate a close functional relationship between the lymphoid and Ia-like antigen positive dermal cells during the pre-malignant phase of cutaneous T cell lymphoma. (Author abstract) (39 Refs)

38. LYMPHOMA.

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Cancer Res. Campaign, Christie Hosp. and Holt Radium Inst., Wilmslow Road, Manchester M20 9BX, England
Cancer Chemotherapy 1981- The EORTC Cancer Chemotherapy Annual 3. Pinedo HM, ed. Amsterdam, Excerpta Medica, 504 pp, 1981.

Literature published in 1980 on the management of lymphoma is reviewed. Treatment of Hodgkin's disease in adults and children is described and salvage chemotherapy discussed. Treatment of non-Hodgkin's lymphoma is reviewed with respect to generalized lymphomas of high-grade pathology, lymphoblastic lymphoma, cutaneous T-cell lymphoma, Burkitt's lymphoma, malignant histiocytosis, generalized lymphomas of low-grade pathology, salvage chemotherapy, immunotherapy, treatment in children, and long-term complications of therapy. (112 Refs)

39. PROSPECTIVE EVALUATION OF THE LEUKOCYTE ADHERENCE INHIBITION (LAI) TEST IN BREAST CANCER USING A PANEL OF EXTRACTS FROM KNOWN AND UNKNOWN PRIMARY TUMORS.

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Int J Cancer; 29(3):261-264 1982

The antigen-induced leukocyte adherence inhibition (LAI) test is an assay of cellular immune reactivity which was expected to offer a promising adjunct to currently available diagnostic and monitoring procedures in cancer patients. We have applied this assay to 83 inpatients clinically suspected of having breast cancer, 50 outpatients before mammography, and 37 healthy women. In order to account for the known heterogenicity of breast cancer, we performed LAI assays with extracts from 15 primary tumors of known and 14 primary tumors of initially unknown histology. Thus, the problem of tumor specificity in the LAI assay was tackled in a double-blind fashion. The results obtained clearly show that breast-tissue-specific rather than tumor-specific responses were detected by LAI testing. The LAI assay failed to discriminate between high-risk patients with and without cancer and between extracts from breast tumors with and without carcinoma. The results are discussed with regard to the many claims for the detection of specific tumor immunity in the literature. (Author abstract) (25 Refs)

40. LYSIS OF FRESH HUMAN SOLID TUMORS BY AUTOLOGOUS LYMPHOCYTES ACTIVATED IN VITRO WITH LECTINS.

Mazumder A, Grimm EA, Zhang HZ, Rosenberg SA
Surgery Branch, NCI, Building 10, Room 10N116, Bethesda, MD, 20205
Cancer Res; 42(3):913-918 1982

Human peripheral blood lymphocytes (PBL), obtained from patients with a variety of cancers, were incubated in vitro with phytohemagglutinin, concanavalin A, and crude or lectin-free T-cell growth factors. The lectin-activated PBL of nine patients were capable of lysing fresh autologous tumor during a 4-hr 51Cr release assay. Multiple metastases from the same patient were equivalently lysed by these activated autologous PBL. No lysis of fresh PBL or lectin-induced lymphoblast cell targets was seen, although tumor, PBL, and lymphoblast cells were shown to be equally lysable using allosensitized cells. The activated cells could be expanded without loss of cytotoxicity in crude or lectin-free T-cell growth factors. The generation of cells lytic to fresh autologous tumor was dependent on the presence of adherent cells, although the lytic cell itself was not adherent. Proliferation was not involved in the induction of lytic cells since equal lysis was induced in irradiated and nonirradiated lymphocytes. Lectin was not required in the lytic assay, and the addition of alpha-methyl-D-mannoside to concanavalin A-activated lymphoid cells did not decrease the lysis of fresh tumor cells. Activation by lectin for 3 days appears to be an efficient and convenient method for generating human cells lytic to fresh autologous tumor. These lytic cells may be of value for studies of the cell-mediated lysis of human tumor and possibly for tumor immunotherapy as well. (Author abstract) (29 Refs)

41. SUPPRESSION OF NATURAL CELL-MEDIATED CYTOTOXICITY IN MAN BY MATERNAL AND NEONATAL SERUM.

Barrett DS, Rayfield LS, Brent L
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Clin Exp Immunol; 47(3):742-748 1982

The natural cytotoxicity of cells prepared from the blood of human neonates and women at the time of parturition was investigated, using a 4 hr 51Cr release assay and two established cell lines as targets. Although cord cells proved to be cytotoxic, the overall level was distinctly lower than of normal adult cells. Whereas adult cells from males gave higher levels of cytotoxicity compared with cells from females, this was not the case for cord cells. Cells from women in labor showed even lower cytotoxic values. Neonatal and maternal serum or plasma caused a profound inhibition of the cytotoxicity shown by adult cells when present during the assay or following preincubation of effector cells with serum. Cord cells were not suppressed by either autologous or allogeneic cord sera. The nature of these suppressive factors and their origin and ontogeny remain to be elucidated. It would appear that in the neonate, and possibly also in the fetus, natural cytotoxicity is largely suppressed by serum factors, both in mother and offspring. This could represent yet another example of immunological modulation in pregnancy. (Author abstract) (14 Refs)

42. INFLUENCE OF LOCAL FACTORS ON THE GROWTH OF TUMORS.

Taradi M
Zavod za fiziologiju Medicinskog fakulteta Sveucilista u Zagrebu, Zagreb, Yugoslavia
Lijec Vjesn; 103(4/5):212-213 1981

Influence of local factors on tumor growth is discussed. Intracellular reactions have an important role in growth regulation, and changes in intercellular communications could cause or express the neoplastic process. Chalones, angiogenesis, and nonspecific macrophage reactions are also important factors of the microenvironment influencing the tumor growth. (30 Refs) (In SCR)

43. ROLE OF MONOCYTES, ALLOANTIGENS, AND INDIVIDUAL REACTIVITY IN THE RESPONSE OF HUMAN LYMPHOCYTES TO MITOGENIC FACTOR.

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J Immunol; 128(3):1289-1295 1982

The activity of mitogenic factors generated in human mixed lymphocyte cultures (MLC-MF) was analyzed with unstimulated mononuclear leukocytes used as responder cells. Unseparated or adherent, but not nonadherent, irradiated, autologous mononuclear leukocytes were found to significantly enhance the mitogenic activity of MLC-MF. The effect of MLC-MF was not inhibited by hydrocortisone at concentrations that inhibited MLC-MF production, indicating that the MLC-MF effect is direct and is not mediated through further production of mitogenic factors. Experiments in which MLC-MF was produced in a MLC between a HLA-D homozygous individual and her child suggested that soluble alloantigens do not play a role in the MLC-MF effect. Studies in one individual with MLC responses higher than other individuals indicated av MLC-MF production but above av response to MLC-MF. We conclude that MLC-MF is directly mitogenic for unstimulated lymphocytes, without requiring the simultaneous presence of either mitogen or antigen. In addition, the proliferative MLC reaction of individuals with strong responses to MLC-MF may be influenced significantly by the nonspecific clones recruited by MLC-MF. (Author abstract) (22 Refs)

44. IN-SITU T LYMPHOCYTE IDENTIFICATION IN CUTANEOUS TISSUE SECTIONS OF BENIGN AND MALIGNANT DERMATOSES.

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Histopathology; 6(1):25-33 1982

An indirect immunoperoxidase reaction was used to identify T-lymphocytes in situ in cutaneous tissue sections of a variety of benign and malignant dermatoses from patients. Except for sarcoidosis, follicular lymphoma, and multicentric reticulohistiocytosis, many of the cells present in the cutaneous infiltrate of the tissue samples were shown to be T-lymphocytes. In sarcoidosis, follicular (B-cell) lymphoma, and multicentric reticulohistiocytosis where the predominant cell types were epithelioid cells, B-lymphocytes, and histiocytes, respectively, only a few T-lymphocytes were found. Expected paucity of T-cells in the latter three tissue sections indicates the specificity of the anti-serum used. The method is a relatively simple way to identify T-lymphocytes and has advantages over other methods now in use. (25 Refs)

45. EVALUATION OF ANTIBODY-DEPENDENT CELL CYTOTOXICITY (ADCC) AND SPONTANEOUS LYMPHOCYTE-MEDIATED CYTOTOXICITY (SLMC) IN PATIENTS SUFFERING FROM MALIGNANT DISEASE.

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G Clin Med; 62(9):609-623 1981

The immune system and the evolution of malignant neoplasia were studied in 36 patients with cancer. Lymphocytes B, T, and EA rosette formation were determined in normal controls (NC: 20-70 yr old patients) with different diseases (DD), with localized cancer (LC: pulmonary, mammary, digestive tract, melanomas etc), with metastasizing cancer (MC: mammary cancer with bone and brain metastases, colon cancer with hepatic metastases and bladder cancer with bone and lymph node metastases), patients receiving polychemotherapy (PCT) with 5-fluorouracil and dacarbazine, patients receiving cyclophosphamide (CYP), and patients receiving radiotherapy (RT). Antibody-dependent cell cytotoxicity (ADCC) and spontaneous lymphocyte-mediated cytotoxicity (SLMC) were present in all NC with values slightly lower in older persons and women.

The values for lymphocytes B, T, and EA rosette for NC were on the av 10%, 55%, and 8%, respectively, for DD the values were 8%, 53%, and 7% respectively, for not treated LC the values were 7%, 47%, and 7%, respectively, for not treated MC were 8%, 41%, and 6% respectively, for PCT were 7%, 38%, and 6%, respectively, for treated with CYP the values were 4%, 22%, and 3%,respectively, and for treated with RT the values 2%, 7%, and 2%, respectively. Natural Killer cell activity was significantly decreased in MC patients. Differences of lytic response in vitro were not related to T/B lymphocyte ratio in 90% of the cases. (5 Refs) (In ITA)

46. HUMAN T-CELL MALIGNANCIES: CORRELATIVE CLINICAL, HISTOPATHOLOGIC, IMMUNOLOGIC, AND CYTOCHEMICAL ANALYSIS OF 23 CASES.

Knowles DM, Halper JP
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Am J Pathol; 106(2):187-203 1982

Twenty-three T-cell neoplasms were investigated for their reactivity with the OKT monoclonal antibodies and expression of certain cytochemical markers. Fourteen neoplasms with diverse histopathologic features, T-cell chronic lymphocytic leukemia, mycosis fungoides, the Sezary syndrome, T-immunoblastic sarcoma, and a pleomorphic large-cell lymphoma, expressed the T helper cell phenotype, OKT3T4. Nine other neoplasms displayed marked inter- and intra-tumor heterogeneity. Seven of these cases, lymphoblastic lymphoma, T-cell acute lymphoblastic leukemia, and tumors with features of T-immunoblastic sarcoma or the multilobated lymphoma of Pinkus, expressed intrathymic phenotypes. The other two cases, a lymphoblastic lymphoma and a so-called Lennert's lymphoma, expressed the previously undescribed OKT3T10 phenotype. These studies demonstrate that the T-cell malignancies are divisible into phenotypes corresponding to normal maturational stages of T-cell differentiation and functionally distinct T-cell subsets. Such studies should provide a basis for understanding the biologic heterogeneity, clinical diversity, and significance of the variable cytomorphologic characteristics of T-cell malignant tumors and assist in the further delineation of normal human T-cell heterogeneity. (Author abstract) (57 Refs)

47. EFFECTS OF ACTIVATED T CELLS ON NATURAL KILLING.

Knight RA, Fitzharris P
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Immunology; 45(3):513-519 1982

Two populations of human blood lymphocytes, one forming rosettes with sheep erythrocytes, the other non-rosetting, are cytolytic in vitro for several long term cultured tumor-derived cell lines. A particular breast cancer-derived target cell (MDA 157) is only killed by the non-rosetting effector. Rosetting cells from normal donors infected or immunized with influenza virus augment cytolytic activity on MDA-157 targets by non-rosetting effector cells. Similar augmenting activity can be induced by incubating the rosetting population with sources of immune (gamma), but not leukocyte (alpha) interferon in vitro. This augmentation of cytolytic activity does not require compatibility at the major histocompatibility locus between the augmenting and effector populations. (Author abstract) (22 Refs)

48. HUMAN E-ROSETTE-POSITIVE CELLS WHICH BIND MONOMERIC IGG MEDIATE NATURAL CYTOTOXICITY.

Froelich CJ, Tai AS, Bankhurst AD, Warner NL
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Cell Immunol; 66(1):190-194 1982

We have observed that a subset of E cells bind human monomeric IgG (FcR-IgG). In the present study, we have separated the E, FcR-IgG cells by flow cytometry and tested their NK activity against the tumor K562 using the chromium-release assay. Virtually all the NK activity residing within the E subset was mediated by E, FcR-Ig cells. These findings are discussed in relation to the cellular lineage of the human NK cell. (Author abstract) (14 Refs)

49. AUTOLOGOUS MIXED LYMPHOCYTE REACTION IN HUMAN CORD BLOOD LYMPHOCYTES: DECREASED GENERATION OF HELPER AND CYTOTOXIC T-CELL FUNCTIONS AND INCREASED PROLIFERATIVE RESPONSE AND INDUCTION OF SUPPRESSOR T CELLS.

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Cell Immunol; 66(1):88-98 1982

T lymphocytes from neonates proliferated significantly more than peripheral blood T lymphocytes from adults in autologous mixed lymphocyte reactions (AMLR). AMLR-activated cord, as compared to adult T lymphocytes, exerted significantly less nonspecific cytotoxic activity on PHA-stimulated adult mononuclear cells and Epstein-Barr virus-transformed target cells. The impaired generation of cytotoxicity of cord T cells was not corrected by Interleukin-2. Blood T lymphocytes form adults activated in AMLR synthesized a helper factor that supported PWM-induced proliferation and immunoglobulin production in both adult and cord B lymphocytes. In contrast, cord blood T lymphocytes failed to produce the helper factor for B lymphocytes. T cells from AMLR cultures established with neonatal lymphocytes showed suppressor activity, as assessed in PWM-stimulated immunoglobulin synthesis of adult peripheral-blood mononuclear cells, significan tly higher than that exhibited by T cells from AMLR cultures performed with lymphocytes from adults. Finally, neonatal B lymphocytes could be activated to the production of IgM but not IgG by either adult AMLR-derived helper factor plus PWM or by Epstein-Barr virus, whereas adult B cells secreted both IgM and IgG under the same type of stimulation. (Author abstract) (35 Refs)

50. STIMULATION OF HUMAN LYMPHOCYTES WITH IRRADIATED CELLS OF THE AUTOLOGOUS EPSTEIN-BARR VIRUS-TRANSFORMED CELL LINE. II. CYTOTOXIC RESPONSE TO REPEATED STIMULATION.

Allen DJ, Rickinson AB, Wallace LE, Rowe M, Moss DJ, Epstein MA
Dept. Pathology, Medical Sch., Univ. Bristol, Bristol BS8 1TD, England
Cell Immunol; 67(1):141-151 1982

Unfractionated peripheral blood mononuclear (UM) cells from adult donors of known serological status with respect to Epstein-Barr (EB) virus were exposed to four or more successive in vitro stimulations with irradiated cells of the autologous

EB virus-transformed cell line at a responder:stimulator ratio of 4:1, and effector UM and T cells were prepared after each stimulation. Ten out of 14 seropositive donors and all four seronegative donors thus tested showed at best moderate cell proliferation over two or three stimulations only and a cytotoxic response which became dominated by non-E-rosette-forming cells active against the K562 cell line but not against EB virus-transformed lymphoblastoid lines. Cocultures from three other seropositive donors gave stronger proliferative responses and yielded effector cells dominated by a polyclonal E-rosette-forming population cytotoxic to the autologous and to certain allogeneic (both HLA-related and -unrelated) EB virus-transformed cell lines as well as to some but not all EB virus genome-negative hemopoietic cell lines of the kind sensitive to natural killer cells. With one other seropositive donor, this same repeated stimulation induced a quite different type of cytotoxic response, selectively amplifying an effector T-cell population which appeared on the basis of target cell specificity and of sensitivity to monoclonal antibody blocking to be both EB virus-specific and HLA-A and B antigen restricted in its function. (Author abstract) (32 Refs)

51. ASSESSMENT OF THE IN VITRO RADIOSENSITIVITY OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES.

Knox SJ, Shifrine M, Rosenblatt LS
Lab. Energy-Related Health Res., Univ. California, Davis, Davis, CA, 95616
Radiat Res; 89(3):575-589 1982

Sensitivities of different assay methods used to study the effects of low-level (sublethal) in vitro x-irradiation on lymphocytes were evaluated. Sensitive lymphocyte progenitor cells from 31 clinically normal adults were evaluated for proliferative capacity following in vitro x-irradiation at 0-400 R. Dose-response studies were conducted using human whole blood and gradient-separated lymphocyte enriched mononuclear cell fractions in the lymphocyte stimulation test (LST) and colony formation assay (Col) with six different mitogens/antigens. Assays using whole blood were able to detect radiation effects at lower doses than assays using gradient-separated cells. Col was consistently more sensitive than LST with mitogen/antigen groups. Survival curves for subjects based on LST results were characterized by a typical dose-response curve with a shoulder at lower doses followed by a single-exponential decrease in survival; the number of colonies relative to dose followed a two-exponential curve lacking a shoulder at lower doses. The assays are potentially applicable to assessment of the relative radiosensitivity of lymphocytes and associated risk for radiation-induced leukemogenesis of different population groups with immunologic and hematologic abnormalities. (46 Refs)

52. DEFECTIVE MACROPHAGE-T-CELL INTERACTION IN COMMON VARIED IMMUNODEFICIENCY.

Eibl MM, Manhalter JW, Zielinski CC, Ahmad R
Inst. Immunology and II. Dept. Medicine, Univ. Vienna, Vienna, Austria
Clin Immunol Immunopathol; 22(3):316-322 1982

Macrophage-T-cell interaction (MTI) was studied in 9 patients with common varied immunodeficiency (CVID) and in 23 healthy control individuals. Adherent cells of patients and of controls were pulsed with Escherichia coli and subsequently cultured with autologous T-cell-enriched populations (TCE). The proliferative response of the TCE population was estimated by measuring [3H]thymidine incorporation after a 7-day culture period. Mean values in controls were 22,852 dpm -3263, in patients 3,284 -1,420, respectively (p less than 0.001). Eight of nine patients showed reduced proliferation on the 7th day, in two patients TCE population proliferated with a different kinetic (peak on the 11th day), while MTI of the remaining six patients stayed low. We suggest that defective MTI may contribute to defective immunoglobulin production in CVID. (Author abstract) (28 Refs)

53. AN IMMUNOPEROXIDASE STUDY OF CYTOMEGALOVIRUS MONONUCLEOSIS.

Abramowitz A, Livni N, Morag A, Ravid Z
Dept. Pediatrics, Hadassah-Hebrew Univ. Medical Center, P.O. Box 12,000, Jerusalem, Israel
Arch Pathol Lab Med; 106(3):115-118 1982

Indirect immunoperoxidase method was used to evaluate retrospectively a case of cytomegalovirus (CMV) mononucleosis. Specific rabbit antiserum against CMV was used as primary reagent in routinely prepared paraffin sections of lymph node and in fixed slide preparations of the bone marrow aspirate. Staining specific for CMV antigen was observed in the lymphoid cells of the lymph node in the predominantly T-cell area and in the large lymphoid cells of the bone marrow. Bone marrow lymphoid cells with morphologic characteristics similar to those of the cells positive for CMV antigen showed positive immunoperoxidase reaction with specific rabbit antihuman T-cell serum. The data strongly indicate that CMV antigen was localized predominantly in the cells of lymphoid origin during the acute stage of the CMV mononucleosis; some data also suggest that infected lymphoid cells may be of T-cell origin. An immunoperoxidase technique is advantageous in both diagnosing and evaluating CMV mononucleosis. (Author abstract) (24 Refs)

54. IMMUNOTHERAPY OF TUMORS.

Baldwin RW
Cancer Res. Campaign Laboratories, University Park, Nottingham NG7 2RD, England
Cancer Chemotherapy 1981- The EORTC Cancer Chemotherapy Annual 3. Pinedo HM, ed. Amsterdam, Excerpta Medica, 504 pp, 1981.

Aspects of present-day immunotherapy are reviewed and some additional basic information on interferons is presented. Areas discussed are active specific immunotherapy, natural resistance to tumors (natural killer cells, macrophages), immunomodulating agents (BCG, methanol extraction residue, cell-wall preparations, muramyl dipeptide, Corynebacterium parvum, and interferon), immunostimulating compounds, and antibody-directed cytotoxic agents. (166 Refs)

55. THE HUMAN INTERFERON SYSTEM.

Berman B, Frankfort HM
Dept. Dermatology, Mount Sinai Sch. Medicine, 1 Gustave L. Levy Place, New York, NY, 10029
Int J Dermatol; 21(1):12-18 1982

Clinical uses of interferon (IF) in dermatology are reviewed. IF inhibits both DNA- and RNA-containing viruses, as well as nonviral intracellular organisms. The immunomodulatory effects of IF on phagocytosis, histamine, prostaglandin E, antibody dependent cell-mediated cytotoxicity, natural killer lymphocytes, and mitogen activation of lymphocytes are discussed. Clinical studies of IF in cases of herpes zoster, varicella, herpes simplex, vaccinia, congenital rubella, condylomata acuminata and malignant melanoma are discussed. (85 Refs)

56. MALNUTRITION AND POSTOPERATIVE INFECTIONS IN THE NEOPLASTIC PATIENTS.

Dionigi P, Nazari S, Bonoldi A, Tibaldeschi C, Olezza S, Dionigi R
Istituto di Patologia Speciale Chirurgica, Universita di Pavia, 27100 Pavia, Italy
Minerva Chir; 36(21):1423-1431 1981

Malnutrition and infections after surgery were evaluated in 58 patients (19 men, 39 women; 13-80 yr old) with cancer (20 mammary, 11 colorectal, 9 gastric, 4 esophageal, 4 lymphomas, and 10 others). The patients had wound (14), respiratory (10), urinary (9), peritoneal (3) and (2) others infections. Controls were 21 patients (17-79 yr old) with different benign pathologies who underwent minor surgery. Complete nutritional assessment wt, arm circumference, Hb, albumin, ceruloplasmin, retinol binding protein, urinary creatine, immunological status, leukocytes, lymphocytes, delayed hypersensitivity response with tuberculin, trichophyton, Candida albicans, and dinitrochlorobenzene as primary antigen were measured before surgery in cancer patients, and in controls. The ceruloplasmin levels were (49 -10 mg% in the patient with septi cancer, 43 - 8.5 mg% in the patient with non-septic cancer, and 38 -4.2 mg% in controls) the only significant indicators of postoperative infections. Length of time under anesthesia, contamination of the operating room, and stage of cancer (important factors) were examined. (40 Refs) (In ITA)

57. IN VITRO IMMUNIZATION AS A METHOD FOR GENERATING CYTOTOXIC CELLS POTENTIALLY USEFUL IN ADOPTIVE IMMUNOTHERAPY.

Mokyr MB, Dray S
Dept. Immunology and Microbiology, Univ. Illinois at the Medical Center, Chicago, IL, 60612
Methods Cancer Res; 19:385-417 1982

The following aspects of utilization of in vitro immunized lymphoid cells in therapy are reviewed, based on studies in several mouse systems: critical factors for the success of in vitro immunization, optimal source of responder and stimulator cells, methods to potentiate the antitumor activity of in vitro immunized cells, methods to screen in vitro immunized cells for their immunotherapeutic potential, and the advantages of using in vitro immunized lymphoid cells as an adjunct to chemotherapy. In vitro immunized lymphoid cells were therapeutically superior to in vivo immunized lymphoid cells in a number of ways. Therapy with adoptively transferred cells may be improved by growing large numbers of cytotoxic cells in vitro, and repeatedly administering these cells to help maintain large numbers of cytotoxic cells within the system. The apparent role of adoptively transferred immune cells is to extend the period of time in which the concentration of tumor cells is low, allowing the recipient to develop strong antitumor immunity to cope with the remaining tumor cells. (157 Refs)

58. THE HANDBOOK OF CANCER IMMUNOLOGY, VOLUME 7. IMMUNE FUNCTION AND DYSFUNCTION IN RELATION TO CANCER.

Waters H
NIH, Bethesda, MD
The Handbook of Cancer Immunology, Volume 7. Immune Function and Dysfunction in Relation to Cancer. New York, Garland STPM Press, 372 pp., 1981.

Aspects of immune function and dysfunction as they relate to cancer are presented. Immunological surveillance is discussed with consideration of the thymus, macrophages, cytotoxic cells, and immunodepression in cancer patients. Immune responses to challenge, including cellular and humoral factors, and the role of these factors in immune suppression are considered. Other topics include regulation of immune response, immunobiology of chemotaxis and metastases, and the role of macrophages and other cells in carcinogenesis. Macrophage arginase and arginine consumption are related to tumor growth. Also discussed are rejection and enhancement of grafts, the role of antigens and antibodies in idiotype regulation and T-lymphocyte modulation, immunoregulation via modified amino groups, immunity and tolerance t o transplantation antigens, and production of specific unresponsiveness to tissue allografts by immunosuppression and donor antigen. Normal and abnormal conditions, as well as intermediate conditions are compared. Discussion of topics includes review, original findings, and speculation about future investigative efforts. (1420 Refs)

59. IMMUNOLOGICAL SURVEILLANCE AND CANCER.

Stutman O
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

Analysis of the available evidence on the effects of experimental or clinical immunodeficiency on cancer incidence shows that the orthodox immunosurveillance theory (ie, mediated by a thymus-dependent effector cell system capable of destroying nascent tumors) is wrong. The incidence of most tumors is not increased in thymus-dependent immune deficiencies. Immunosurveillance of a 'nonadaptive' nature may be involved. Macrophages and the non-macrophage natural killer (NK) and natural cytotoxic (NC) cells, which are cytotoxic to tumor cells without specific preimmunization, may be involved in surveillance mechanisms in vivo. These responses may act as putative surveillance devices against non-antigenic tumors, although they are probably not directed against conventional tumor-associated antigens. The fact that most clinical tumors seem to be monoclonal argues against a highly efficient surveillance by either the macrophages or the NK-NC cell system. Procedures interfering with or potentiating macrophage or natural cell-mediated cytotoxicity may provide additional evidence of the efficiency (even the existence) of these in vivo defenses against tumors. Experimental or clinical models of selective deficiencies of macrophage or cell-mediated cytotoxicity may provide additional information. Future research should probably involve experiments designed to determine whether or not immunologic surveillance is mediated by some other mechanism(s). (136 Refs)

60. IMMUNOSUPPRESSION IN NEOPLASIA.

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Mayo Medical Sch., Rochester, MN, 55901
The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

An immunologic challenge elicits the formation of cells and factors which both enhance and suppress (or terminate) the immune reaction. The net result of the challenge depends on the ratios of these enhancing and inhibitory signals. There is evidence for an association between immunosuppression and neoplasms, but it is not clear whether the immunosuppression is required for tumor establishment (or tumor growth) or a secondary event. Some soluble immunosuppressive factors have been isolated from sera and t umors, but more evidence is needed as to their natures and activities. The possibility that a virus may be responsible for the activity of suppressor cells has not always been excluded. Antigen-specific suppressor T cells are clearly involved in the establishment of tumors. The role of nonspecific suppressor cells is less clear, especially in view of the finding that tumor-bearing animals with elevated levels of nonspecific suppressor cells are not always immunologically comprised. A good correlation has been established between anergy and the presence of soluble immunosuppressive factors (not yet purified) in cancer patients. However, immunosuppression has not been discovered in all or even most cancer patients, and 33% of all cancer patients do not show elevated levels of the immunosuppressive factors which can now be analyzed. These findings suggest that immunosuppression is not a general phenomenon in human cancer and therefore not a requirement for tumor development. However, it is possible that immunosuppressive elements may act locally at the tumor site. Currently used tests of immune function may not detect subtle but important abnormalities. Future research should provide both a better understanding of both immune regulation in neoplasia and normal immune homeostatic mechanisms. (124 Refs)

61. REGULATION OF THE IMMUNE RESPONSE.

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The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

The functions of T-cells, B-cells, the macrophage-monocyte series, and subpopulations of T-cells (including helper and suppressor T-cells) and B-cells can be elucidated by the use of a series of selectively acting mitogens. Soluble factors isolated from activated B- and T-cells can act as mitogens in the reciprocal cell type. The other side of cellular activation is specific immunologic unresponsiveness. Suppressor T-cells are transiently demonstrable in states of immunologic tolerance to protein antigens, but they are neither necessary nor sufficient for the induction or maintenance of the tolerant state. The B- and T-cells require different amounts of tolerogen for the induction and maintenance of self-tolerance. This type of immunologic tolerance is more easily maintained at the T-cell level. Tolerance to self-antigens is largely maintained at the T-cell level. Different cellular mechanisms have been discovered in different types of experimental autoimmune diseases. Some of these diseases are attributable to the actions of B-cells (in the presence of adequate T-cell help or T-cell bypass). In other cases, the induction of autoreactive T-cells seems to be entirely responsible for the genesis of some autoimmune diseases. (229 Refs)

62. PERSPECTIVES: MECHANISMS OF LYMPHOCYTE-ANTIGEN INTERACTIONS.

Nossal GJ
Walter and Eliza Hall Inst. Medical Res., Melbourne, Australia
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

After an antigen is recognized by the B- or T-lymphocytes, lymphocyte activation normally requires a second 'signal' from a macrophage or helper T cell. If the second signal is absent, the result is often immunologic tolerance, especially if the cell is immature. The first phase of the lymphocyte interaction with any tumor-associated transplantation antigens (TATA) of a human tumor may be an antibody formation and a delayed hypersensitivity. However, the weakness of the TATA will probably lead to an immune attack too weak to reject the tumor. The fact that nude mice do not show a substantially increased incidence of spontaneous tumors suggests that actively acquired T-cell-dependent immunity may not be a major defense against cancer. Factors working against an effective immune defense or immunotherapy in the presence of a growing tumor include the formation of soluble antigen-antibody complexes (which have a potentially tolerogenic effect on T- and B-cells), the formation of increasing amounts of free soluble antigen, the genetic selection of immunologically resistant tumor cells, and the generalized immunosuppression (especially in the T-lymphocyte compartment) accompanying cachexia. As knowledge of human tumor antigens improves and as monoclonal antibodies become available, the targeted 'missile' approach to treatment (using radiolabeled or drug-bound antibody) will increase. However, the ultimate place of immunologic intervention in cancer therapy will probably be limited, in view of the definite quantitative limits to the immune system's ability to deal with tumor cells even in favorable model systems. (47 Refs)

63. PERSPECTIVES: THE EVOLUTION OF IMMUNE RESPONSES AND CANCER.

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Dept. Human Morphology, Univ. Nottingham Medical Sch., Queen's Medical Center, Nottingham, NG7 2UH, England
The Handbook of Cancer Immunology: Volume 9- Humoral Immunity in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 289 pp., 1981.

In invertebrate animals, phagocytosis or encapsulation are the defenses against non-self materials. Natural or inducible humoral factors, possibly having a supplementary protective action, are present in higher invertebrates. Because true malignancies occur in invertebrates, the capacity for tumorigenesis apparently arose before the capacity to mount immunologic defenses based on immunoglobulins. Studies on the development of the thymus gland and cell-mediated immunity in nonmammalian vertebrates suggest that the thymus and T-lymphocytes are a comparatively recent evolutionary development. Malignancies comparable to those of birds and mammals have been found in all classes of ectothermic vertebrates. (188 Refs)

64. SPECIFICITY AND ROLE OF ANTIBODIES TO TUMOR ASSOCIATED ANTIGENS: ONE VIEW FROM THE LABYRINTH.

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Tumor Biology Unit, Dept. Pathology, Coll. Medicine, Univ. Florida, Gainesville, FL, 32610
The Handbook of Cancer Immunology: Volume 9- Humoral Immunity in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 289 pp., 1981.

Animals bearing some types of tumors develop antibodies in response to tumor-associated antigens (TAAs). The net results of the host-tumor-TAA interaction range from inhibition to promotion of local tumor growth and metastatic spread. The natures of these TAAs are poorly understood. Cell-mediated mechanisms depend on T-lymphocytes are important in host reactions to immunogenic transplantable tumors. Only highly immunogenic tumors induced by certain DNA viruses elicit immune surveillance reactions Because of the major differences between transplantable animal tumors and spontaneous human tumors, the applicability of these studies on tumor immunology to clinical research is not clear. (91 Refs)

65. RECENT ADVANCES IN CANCER CYTOGENETICS.

Pogosiants EE
All-Union Cancer Res. Center, Moscow, USSR
Genetika; 17(12):2087-2099 1981

Recent studies in the field of cancer cytogenetics are reviewed with special emphasis on karyotypic changes in leukemia and carcinoma cells, prezygotic chromosome mutations specific for certain human tumors, and phenomena of gene amplification characteristic for a number of tumors and for cells resistant to antineoplastic agents. Specific karyotypic changes were observed in human and murine leukemias, as well as in a number of experimental sarcomas and carcinomas. Specific involvement of chromosome 15 was recorded in murine radiation-induced and carcinogen-induced T-cell leukemias; also, trisomy for chromosome 15 or translocation involving chromosome 15 were detected in B-cell leukemias and lymphomas. Specific involvement of the distal third of chromosome 15 indicated that this region contains the cluster of genes responsible for normal differentiation and malignant transformation of lymphoreticular cells. Specific prezygotic chromosome aberrations were observed in retinoblastoma (deletion in the long arm of chromosome 13), nephroblastoma (deletion in the short arm of chromosome 11), and in familial kidney carcinoma (translocation between chromosomes 3 and 8). Specific resistance of eukaryotic cells to methotrexate was shown to be associated with the presence of homogenously stained regions and the number of double microchromosomes. (73 Refs) (In RUS)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

66. INHIBITION OF EXPERIMENTAL TUMOR METASTASIS BY SELECTIVE ACTIVATION OF NATURAL KILLER CELLS.

Hanna N
Smith Kline and French Lab., 1500 Spring Garden St., P. O. Box 7929, Philadelphia, PA, 19101
Cancer Res; 42(4):1337-1342 1982

The antitumor activity generated by selective activation of natural killer (NK) cells was studied in vitro and in vivo. Unlike Corynebacterium parvum CN6134, which activated both NK cells and macrophages, periodate-oxidized C parvum CN6134 lost the ability to activate macrophages but retained almost all the NK-stimulating capacity of the untreated bacterium. The 'inactive' C parvum strain CN5888 also induced a modest, but selective, activation of NK cells. The enhanced NK cell-mediated cytotoxicity was expressed against YAC-1 lymphoma, UV-2237 fibrosarcoma, and B16 melanoma target cells in vitro and was manifested in vivo by increased destruction of circulating tumor cells and the inhibition of hematogenous tumor metastasis. Periodate-treated C parvum was as effective in inhibiting the formation of B16 melanoma pulmonary metastases as was untreated C parvum. In both cases, the inhibiting effect corresponded closely with the kinetics of NK cell activation. (Author abstract) (28 Refs)

67. INFLUENCE OF NUCLEIC ACIDS ISOLATED FROM ASCITIC FLUID OF EHRLICH TUMOR ON SURVIVAL.

Belokhvostov AS, Grikurova NK
N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 27(12):56-59 1981

The effect of nucleic acids isolated from ascitic fluid of Ehrlich tumor and Zaidela's hepatoma on the survival rate of C3Ha mice inoculated with Ehrlich tumor cells was studied. While nucleic acid preparations suppressed the cytotoxicity of immune lymphocytes in vitro, they failed to increase frequency of tumor inoculation in vivo. The addition of nucleic acid preparation to tumor cells mixed with syngeneic lymphocytes did not block immune defense against tumor growth either. The differences in the effects of nucleic acid preparations in vivo and in vitro are discussed. (Author abstract) (7 Refs) (In RUS)

68. ANALYSIS OF TUMOR PROGRESSION AND IMMUNE SUPPRESSION BY IN VITRO RADIOACTIVE LABELING OF PLASMA SAMPLES.

Alonso G, Rieber M
(c/o Rieber) Center of Microbiology and Cell Biology, Instituto Venezolano de Investigaciones Cientificas, Apartado 1827, Caracas, Venezuela
Cancer Biochem Biophys; 5(4):247-251 1981

Female C57/B1 inbred mice were inoculated with syngeneic EL-4 lymphoma cells and 3LL Lewis lung carcinoma cells; the mice receiving 3LL tumors also were treated with cyclophosphamide (Cy: 20 mg/kg) or antilymphocytic serum (0.2 ml ip). High resolution polyacrylamide gel electrophoresis with Coomassie blue stain revealed no differences in plasma sialoglycoproteins labeled in vitro among the 3LL tumor-bearing animals, with or without treatment, or the control. An identical electrophoretic fractionation of similar samples that had been exposed to sodium periodate and further reduced with tritiated borohydride revealed labeling in 50K and 70K regions in Cy-treated animals that were not found in serum from the others. A 140K dalton protein was evident in serum of Cy-treated and untreated tumor-bearing animals, but not in that of controls. Measurements of in vitro protein phosphorylation made with samples collected at 3, 5, 8, 9, and 10 days after inoculation from animals bearing EL-4 lymphoma revealed a labeled 140K dalton protein on the last 2 days which was not detectable in control samples. The results demonstrate the potential of in vitro radioactive labeling of plasma samples for analysis of tumor progression and immune suppression. (6 Refs)

69. IMMUNOLOGICAL RESPONSES TO FED PROTEIN ANTIGENS IN MICE. I. REVERSAL OF ORAL TOLERANCE TO OVALBUMIN BY CYCLOPHOSPHAMIDE.

Mowat AM, Strobel S, Drummond HE, Ferguson A
Dept. Bacteriology and Immunology, Western Infirmary, Glasgow, Scotland
Immunology; 45(1):105-113 1982

Feeding ovalbumin over a wide range of doses is known to reduce subsequent systemic immune responses to parenteral immunization. In the present study, we have fed mice 2 mg and 25 mg ovalbumin (OVA) 2 wk before systemic immunization and followed the resulting humoral antibody and cell-mediated immune (CMI) responses. The results indicate that while 25 mg OVA will reduce subsequent IgM, IgG and CMI responses to OVA, feeding 2 mg OVA will only suppress CMI responses and to a lesser extent the IgM response. Furthermore, the tolerant state induced by feeding 25 mg OVA was only partially prevented by 100 mg/kg cyclophosphamide (CY) while the suppressed CMI after feeding 2 mg OVA was completely blocked by CY pretreatment. These findings suggest that the humoral and cell-mediated limbs of the immune response may be controlled by different regulatory systems after feeding antigen, and that activation of these systems is dependent on the dose of oral antigen used. In addition, the results are in agreement with our previous finding that CY pretreatment will allow the development of CMI in the gut and gut-associated lymphoid tissue (GALT) after oral OVA and suggest that this phenomenon is related to breakdown of oral tolerance induction. (Author abstract) (34 Refs)

70. CELLS MEDIATING GRAFT REJECTION IN THE MOUSE. II. THE LY PHENOTYPES OF CELLS PRODUCING TUMOR ALLOGRAFT REJECTION.

Loveland BE, McKenzie IF
Dept. Pathology, Univ. Melbourne, Parkville, Victoria, 3052, Australia
Transplantation; 33(2):174-180 1982

The particular T cell subsets involved in the rejection of tumor allografts were examined in mice using two different approaches. In the first, EL4 lymphoma cells or B16 melanoma cells were given to ATXBM-CBA/H mice which had been reconstituted with either naive or sensitized T cells selectively depleted with either Ly-1 or Ly-2 monoclonal antibodies. In mice receiving nonsensitized T cells, Ly-123 cells and to a lesser extent Ly-1 cells were involved in the rejection of both tumors; Ly-23 cells played no role in this rejection. By contrast, in mice receiving sensitized cells, rejection was mediated by Ly-1 cells and not by Ly-123 or Ly-23 cells. In a second approach, sensitized cells were mixed with the tumor cells prior to injection into mice (the Winn neutralization assay). In this case, Ly-123 cells were the prime mediators of graft rejection. We conclude that both Ly-1 and Ly-123 cells can act as mediators of graft rejection. Ly-1-sensitized cells probably act as in a delayed-type hypersensitivity (DTH) response where few lymphocytes can lead to the rejection of many cells. In addition, Ly-123 cells can act as killer T cells but large numbers and the close apposition with the target cells are required. Our results also demonstrate a requirement for Ly-123 precursor cells in nonsensitized mice, probably acting as precursors for both types of effector cell. (Author abstract) (14 Refs)

71. STUDIES OF THE MECHANISMS FOR THE INDUCTION OF IN VIVO TUMOR IMMUNITY. VI. INDUCTION OF SPECIFIC AND NONSPECIFIC CELL-MEDIATED IMMUNITY IN TUMOR-BEARING HOSTS AND ITS CORRELATION WITH TRANSPLANTATION TUMOR IMMUNITY.

Ting CC, Rodrigues D, Nordan R
Lab. Cell Biology, NCI, Bethesda, MD, 20205
Cell Immunol; 66(1):45-58 1982

Studies were performed to determine the development of cell-mediated cytotoxic response at tumor site in C57BL/6 mice bearing progressively growing FBL-3 ascites leukemia. The effectors isolated from tumor ascites are found to be highly cytotoxic for leukemic target cells. The levels of cytotoxicity obtained with effectors isolated from tumor site are generally higher than those obtained with immune mice. This cytotoxicity is both specific and nonspecific. The specific cytotoxicity against tumor-associated antigen is mainly mediated by T cells and the nonspecific cytotoxicity against unrelated tumor cells is mediated largely by macrophages. The T-cell-enriched preparation did not given significant natural killer activity. When testing the ability of these effectors to produce in vivo immunity against the challenge of FBL-3, it was found that only T cells could confer the transplantation-type immunity, but the immunity was transient. The macrophage-enriched preparation isolated from tumor ascites failed to give in vivo protection. These findings indicate that in FBL-3 system, mice with progressively growing tumor are able to develop immune response against tumor cells. However, this immunity is probably interfered with by a suppressor factor(s) or suppressor cells which restrict their activity to eliminate the tumor cells effectively. (Author abstract) (36 Refs)

72. TUMOR BEARER T CELLS SUPPRESS BCG-POTENTIATED ANTITUMOR RESPONSES. I. REQUIREMENTS FOR THEIR EFFECT.

Hawrylko E
Cellular Immunobiology Section, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cell Immunol; 66(1):121-138 1982

Mice bearing established syngeneic tumors fail to reject them when immunized according to protocols based on optimal conditions for BCG potentiation of specific delayed-type hypersensitivity (DTH) and antitumor immunity. Serum factors from mice bearing either the poorly immunogenic mastocytoma, P815 (MA), or the more antigenic sarcoma, Meth A, have been shown to depress both DTH and antitumor immunity. This report demonstrates that lymphoid cells adoptively transferred from these tumor-bearing hosts also can suppress the efferent and afferent phases of DTH to tumor-specific antigens in both BCG-primed and unprimed syngeneic hosts. Suppressor cells (SC) were detected in spleen, thymus, and lymph nodes draining the tumor site, but not in distant superficial lymph nodes. Maximal suppressor activity appeared 6 days after tumor implantation and wanted by 18 days. Suppression of the afferent phase of both the BCG-primed and unprimed responses was antigen specific; suppression of the efferent phase of the BCG-primed response was also specific but SC could partially suppress the unprimed responses to sheep red blood cells (SRBC). Amputation of 6-day-old tumors resulted in the disappearance of splenic SC within 2 days but did not affect SC in draining lymph nodes. SC suppressed DTH in a dose-dependent manner but even the highest doses tested did not totally eliminate the response. Depression of the peak DTH reaction was not accompanied by significant abrogation of antitumor activity. If, however, SC were transferred during the ongoing antitumor response, immunity was partially suppressed. Efferent-phase SC were sensitive to treatment with anti-Thy 1 sera and complement but were unaffected by B-cell depletion. (Author abstract) (29 Refs)

73. TUMOR BEARER T CELLS SUPPRESS BCG-POTENTIATED ANTITUMOR RESPONSES. II. CHARACTERISTICS OF THE EFFERENT PHASE SUPPRESSOR.

Hawrylko E, Mele CA, Stutman O
Cellular Immunobiology Section, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cell Immunol; 66(1):139-151 1982

T cells (Ts) from BALB/c mice bearing 6-day-old syngeneic Meth A tumors can mediate suppression of the efferent limb of the delayed-type hypersensitivity (DTH) response elicited by immunization with irradiated Meth A cells as well as the augmented response obtained when the immunogen is inoculated into BCG-primed sites. Ts in the spleen are Lyt 1-23 and bear I-J determinants. Their induction is thymus dependent. Hydrocortisone depletes the thymus of Ts but spares Ts in the spleen. Ts are metabolically active and dividing as evidenced by their sensitivity to low doses of cyclophosphamide (CY) (20 mg/kg body wt), a 15-hr pulse with vinblastine (Vbl), and irradiation with 600 rad or more. Ts adhere to Sephadex G-10 columns but are unaffected by treatment with carbonyl iron and magnetism. Their phenotype and mechanism of action appear to be comparable to those of Ts2 cells defined in models of DTH to simple haptens. (Author abstract) (36 Refs)

74. EFFECTS OF SOLID TUMORS ON THE RESISTANCE OF MICE TO VIRAL AND BACTERIAL INFECTIONS.

Bonventre PF, Bubel HC, Michael JG, Nickol AD

Dept. Microbiology, Univ. Cincinnati Coll. Medicine, Cincinnati, OH, 45267

Proc Soc Exp Biol Med; 169(2):165-174 1982

Resistance to bacterial and viral pathogens was studied in immunocompetent and athymic Balb/c mice bearing advanced (15-day) methylcholanthrene-induced fibrosarcoma. LD50 values in normal and tumor-bearing Balb/c and heterozygote mice challenged with encapsulated or unencapsulated strains of Streptococcus pneumoniae were identical. In addition, athymic and immunocompetent mice responded similarly to pneumococcal challenge whether or not they carried the tumor. The tumor enhanced resistance to Listeria monocytogenes by 1.0 log unit in immunocompetent mice. Athymic mice bearing 15-day tumors failed to demonstrate increased resistance to L monocytogenes. Non-tumor-bearing athymic mice were marginally more resistant to L monocytogenes than those bearing 15-day tumors. However, animals bearing 1-day tumors (free of lactic dehydrogenase virus) or terminal stage tumors (25-35 days) showed normal levels of resistance to challenge with L monocytogenes. Balb/c and heterozygote mice bearing the nonimmunogenic D2-7041 tumor (15-day) had enhanced resistance to infection with L monocytogenes. Results show that two murine solid tumors at progressive stages of development do not impair native resistance to infection of either immunocompetent or immunodeficient strains of Balb/c mice. This was evident in situations where humoral immunity, cell-mediated immunity, or a combination of the two is a requirement for recovery. (43 Refs)

75. INTERACTION OF SYNGENEIC HEMATOPOIETIC STEM CELLS AND LYMPHOCYTES IN LEUKEMIC AKR MICE.

Chekanova IuI, Riabova LV

No affiliation given

Biull Eksp Biol Med; 91(12):707-709 1981

To evaluate the effect of T-lymphocytes on colony-formation and differentiation of the hematopoietic stem cells during spontaneous leukemia, female AKR mice were transplanted with syngeneic bone marrow cells alone or in a mixture with lymph node and thymus cells. Analysis of the spleen colonies showed that lymph node and thymus cells from leukemic mice caused marked inhibition of the colony-forming ability of both syngeneic and autologous bone marrow cells. Thymocytes and lymphocytes from healthy mice did not affect the proliferation or differentiation of either normal or leukemic bone marrow. (10 Refs) (In RUS)

76. STUDIES OF THYMOPOIETIN PENTAPEPTIDE (TP5) ON EXPERIMENTAL TUMORS. 1. TP5 RELIEVES IMMUNOSUPPRESSION IN TUMOR-BEARING MICE.

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Cell Immunol; 66(2):217-232 1982

The allogeneic and syngeneic immune responses of tumor-bearing mice (C57BL/6 mice bearing 3LL and DBA mice bearing P815) were evaluated by the cytotoxic lymphocyte precursor unit and MLC. In general, tumor-bearing mice showed slightly enhanced immune responses 4 days after tumor inoculation. This enhanced immune response rapidly declined and about 7-10 days after tumor inoculation, both allogeneic and syngeneic responses were markedly lower than normal. Mice treated with TP5, starting 2 wk before tumor inoculation, retained normal or enhanced allogeneic and syngeneic responses up to 3 wk after tumor inoculation. When this tumor-induced suppressive effect was studied in cell transfer experiments, spleen cells from tumor-bearing mice enhanced the growth of tumors in syngeneic recipients whereas spleen cells from TP5-treated mice inhibited the growth of tumors in syngeneic recipients. Moreover, the spleen cells from TP5-treated mice also showed enhanced cytotoxic activity against tumor cells in vitro. These findings suggest that the tumors, after a transient stimulatory phase, induced immune suppressive mechanisms in the hosts' immune defenses. Treatment with TP5 prevented the development of these immune suppressive effects and spleen cells from TP5-treated tumor-bearing mice inhibited tumor growth in freshly tumor-inoculated recipients. (Author abstract) (23 Refs)

77. STUDIES ON THE MECHANISMS OF THE INHIBITORY EFFECTS OF SERUM THYMIC FACTOR ON MURINE ALLOGRAFT IMMUNITY.

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Cell Immunol; 66(2):360-371 1982

The mechanisms of the inhibitory effect of the serum thymic factor (FTS) on allograft immunity have been studied on both cellular and humoral immune responses of skin allografted mice. FTS-induced suppression of allogeneic skin graft rejection was correlated with a transient diminution of in vivo alloreactive CTL production in the spleen, whereas the generation of allo-anti-H-2 antibodies was not affected. The involvement of suppressor cells in the effect of FTS was supported by the observation that irradiated spleen cells from FTS-treated recipients (bearing a 9-day allograft) suppressed the in vitro CTL generation. (Author abstract) (29 Refs)

78. CHANGES IN SUPPRESSOR, HELPER, AND B-CELL FUNCTIONS IN AGING MICE.

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Cell Immunol; 66(2):372-382 1982

Suppressor, T-helper, and B-cell functions were measured in spleen cells derived from individual mice of varying ages. Suppressor activity was assessed by the ability of test cells to suppress the secondary anti-hapten response of young-adult spleen cells in mixed cultures. T-Helper-cell activity was assessed by measuring the ability of T cells activated with carrier-anti-carrier immune complexes to restore the hapten-primed, T-depleted syngeneic cells. B-Cell activity was assessed by measuring the response to the T-independent antigen DNP-Ficoll. It was found that the suppressor function increased rapidly, reached a peak in middle-aged mice, and remained elevated thereafter. In contrast, T-helper and B-cell functions declined at a constant rate from young adulthood to old age. An exception to this pattern was found in a distinct subpopulation of aged mice, which had splenomegaly and extremely low suppressor, T-helper, and B-cell functions. (Author abstract) (28 Refs)

79. FURTHER CHARACTERIZATION OF THE CELLS INVOLVED IN LEUKOCYTE ADHERENCE INHIBITION WITH MURINE TUMOR EXTRACTS.

Koppi TA, Halliday WJ
Dept. Microbiology, Univ. Queensland, St. Lucia, Brisbane, Queensland 4067, Australia
Cell Immunol; 66(2):394-406 1982

Peritoneal cells from tumor-bearing CBA mice were depleted of either T lymphocytes (by treatment with anti-Thy-1.2 antiserum), lymphocytes with the Ly-1 marker (by anti-Ly-1.1 monoclonal antibody), or macrophages (by an adherence method). Depleted populations were compared with control populations for their ability to react with the corresponding tumor extract in the leukocyte adherence inhibition (LAI) assay. Direct and indirect assays were used, with emphasis on the latter which depends on the formation of a soluble mediator, leukocyte adherence inhibition factor (LAIF). Both Moloney sarcoma virus-induced tumors and transplanted methylcholanthrene-induced tumors were employed and gave similar results. LAI reactivity depended on lymphocytes with the Thy-1 and Ly-1 markers, and on macrophages (syngeneic or allogeneic). These T lymphocytes were shown to be the source of LAIF, the macrophages being required as accessory cells. T lymphocytes were also necessary in the LAIF-responsive indicator cell population. (Author abstract) (27 Refs)

80. THE SYNGENEIC MIXED LEUKOCYTE REACTION IN MICE. I. THE CELLULAR AND GENETIC MECHANISM OF THE SYNGENEIC MIXED LEUKOCYTE REACTION.

Yamashita U, Ono S, Nakamura H
Dept. Immunology, Univ. Occupational and Environmental Health, Sch. Medicine, 1-1 Iseigaoka, Yahatanishiku, Kitakyushu 807, Japan
J Immunol; 128(3):1003-1009 1982

The cellular and genetic mechanism of the syngeneic MLR was studied in mice. In Vitro culture of purified T cells with mitomycin C-treated syngeneic spleen cells induced marked proliferative responses that reached maximum on day 8. The restimulation of in vitro cultured T cells with syngeneic spleen cells induced a secondary type of vigorous response that reached maximum on day 2. The responder cells of the syngeneic MLR were Ly-1 T cells. The responder cells were sensitive to the anti-Lyt-1 serum and C treatment, but were resistant to the anti-Lyt-2 and anti-Lyt-3 serum and C treatment. The stimulator cells of the syngeneic MLR were Ia positive, Thy-1 negative, macrophage-like adherent cells. The stimulator cells were sensitive to the anti-Ia serum and C treatment, but were resistant to the anti-Thy-1 serum and C treatment. T cells responsible for the syngeneic MLR had immunologic memory. F1 T cells selected with spleen cells of one parent were restimulated with spleen cells of the same parent but not with spleen cells of the other parent, suggesting the existence of two distinct T cell subpopulations in F1 animals that can preferentially react with spleen cells of one or the other parent. The induction of the syngeneic MLR was controlled by the I-A subregion of the MHC. All these results are very similar as the antigen-specific T cell response that recognizes antigen in association with the I region products on macrophages. The specificity and mechanism of the syngeneic MLR was discussed from the standpoint of self recognition by T cells. (35 Refs)

81. A CRUCIAL ROLE OF THE H-2 D LOCUS IN THE REGULATION OF BOTH THE D- AND THE K-ASSOCIATED CYTOTOXIC T LYMPHOCYTE RESPONSE AGAINST MOLONEY LEUKEMIA VIRUS, DEMONSTRATED WITH TWO DB MUTANTS.

Stukart MJ, Vos A, Boes J, Melvold RW, Bailey DW, Melief CJ
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J Immunol; 128(3):1360-1364 1982

Previous studies have shown that the CTL response of C57BL/6(B6,H-2b) mice against Moloney leukemia virus is H-2 Db-restricted. In the current paper, we analyze the role of the H-2 Db locus in the CTL response against Moloney virus with two strains of mice carrying a mutation in the H-2 Db locus: B6.C-H-2bm13(bm13) and B6.C-H-2bm14(bm14). The influence of the D locus was seen at two levels. First, neither of the two Db-mutant targets could be recognized by Db-restricted CTL, as demonstrated with B10.A(4R) (Kk Db) and B6 (Kb Db) effector cells. Second, mutation at the Db locus strongly altered the character of the response, either by causing nonresponsiveness (bm 14 effector) or by increasing the Kb-associated component of the CTL response (bm13 effector). These findings indicate that a single genetic element, H-2 D in this instance, determines the restriction specificity and regulates the magnitude of the CTL response. Cold target inhibition studies showed that either the restriction specificities of Dbm13 and Kb in the CTL response to this virus are indistinguishable or that the Dbm12-associated component of bm13 CTL is negligible. Experiments with (B6 x bm13)F1 and (B6 x bm14)F1 hybrid responding cells demonstrated a decisive role of H-2 on the antigen-presenting cells used for restimulation in vitro: primed F1 responding cells mounted CTL responses with the H-2 preference and magnitude of the parental cell type used for restimulation in vitro. Our findings strongly support the notion that Type I MHC molecules regulate the magnitude and specificity of the CTL response against viruses. (Author abstract) (29 Refs)

82. RESTORATION OF IMPAIRED IMMUNE FUNCTIONS IN AGING ANIMALS. V. LONG-TERM IMMUNOPOTENTIATING EFFECTS OF COMBINED YOUNG BONE MARROW AND NEWBORN THYMUS GRAFTS.

Hirokawa K, Sato K, Makinodan T
Dept. Pathology, Tokyo Metropolitan Inst. Gerontology, 35-2, Sakaecho, Itabashiku, Tokyo-173, Japan
Clin Immunol Immunopathol; 22(3):297-304 1982

Seventeen-mo-old female B6C3F1 mice (mean life span, 30 mo) were given 600 R, and grafted with young bone marrow cells and newborn thymic lobes, and their immunologic activities were assessed 11 mo later when they were 28 mo old. The results revealed that the treated mice were superior to the untreated age control mice and almost comparable to 14-mo-old mice, in terms of mitogen response to PHA and Con A, humoral response to sheep red blood cells, and cell-mediated cytolytic response to allogeneic cells. No attempt was made to assess the effect of grafting on life span, as all the mice were used for immunologic studies at 28 mo of age. No difference was observed between the treated and untreated mice in their survival time and tumor incidence at the time of sacrifice. (Author abstract) (20 Refs)

83. TREATMENT OF SPONTANEOUS MURINE METASTASES BY THE SYSTEMIC ADMINISTRATION OF LIPOSOMES CONTAINING MACROPHAGE-ACTIVATING AGENTS.

Fidler IJ, Poste G
Cancer Metastasis and Treatment Lab., NCI - Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer- Achievements, Challenges, and Prospects for the 1980s, Proceedings of an International Conference held in New York, 14-16 September, 1980. Vol. 2, Memorial Sloan-Kettering Cancer Center New York, NY. Burchenal, J. H. and Oettgen, H. F., eds. (New York, Grune and Stratton), 944 pp., 1981.

Multiple iv injections of macrophage-activating factor or muramyl dipeptide encapsulated within multilamellar liposomes, but not the free agents, eradicated spontaneous pulmonary and lymph node metastases arising from B16-BL6 melanoma or K-1735 melanoma primary tumors resected before therapy in mice. The lack of toxic effects of the therapy on normal cells and the susceptibility of tumorigenic cells to tumoricidal macrophages in vitro suggest that liposome-encapsulated macrophage-activating agents may be therapeutically useful against metastases. (39 Refs)

84. RETARDATION AND PROMOTION OF GROWTH OF SPONTANEOUSLY APPEARING TUMORS USING IMMUNE LYMPHOCYTES PREVIOUSLY EXPOSED TO EMBRYONIC ANTIGENS.

Gorczynski RM, MacRae S
Ontario Cancer Inst., Toronto M4X 1K9, Ontario, Canada
Cancer Res; 42(3):784-790 1982

Spleen lymphocytes taken from mice at various stages of pregnancy or growth of sc syngeneic tumor implants have been examined for their ability to cause cytolysis of embryo fibroblasts in culture or to affect the growth of the transplanted tumor cells in vivo. Activity of different lymphoid populations in affecting tumor growth in vivo was correlated with activity in vitro, whether cytolysis (growth inhibition) or blocking of cytolysis (growth promotion) was considered. The evidence favors an important role for lymphoid responses to embryo-associated antigens in the control of spontaneous tumor growth, although one cannot yet rule out a crucial role for the host milieu rather than, or in addition to, host cellular elements being the important feature of this control process. (Author abstract) (29 Refs)

85. ANTI-TUMOR IMMUNITY IN B-LYMPHOCYTE-DEPRIVED MICE. III. IMMUNITY TO PRIMARY MOLONEY SARCOMA VIRUS-INDUCED TUMORS.

Gordon J, Holden HT, Segal S, Feldman M
Weizman Inst. Science, Rehovot, Israel
Int J Cancer; 29(3):351-357 1982

Tumor induction and immunity to tumors were studied following the injection of Moloney sarcoma virus (MSV) into mice whose B-lymphocyte functions had been suppressed by the chronic administration of anti-IgM antibodies. Two preparations of MSV were used, one which gives rise to tumors which uniformly regress in normal adult mice, and another which elicits progressively growing tumors in the majority of recipients. The tumor incidence, mean tumor size, and tempo of regression were not modified by treatment with anti-IgM. However, whereas tumors induced by the regressor virus were all rejected in 19 NRG-treated and 29 untreated recipients, continued growth was obtained in 2 of 23 B-lymphocyte-deprived mice. Furthermore, in nine additional mice from this group, apparent rejection was followed by tumor recurrence at the site of the initial tumor. Continued growth was accompanied by widespread metastasis. These tumors were freely transplantable to normal syngeneic recipients. Metastasis and transplantability were also detected in 7 of 24 anti-IgM-treated mice given progressor virus, but were not seen in the control animals. Recurrence and metastasis was obtained despite the presence of high levels of specific cytotoxic T lymphocytes in the spleen. It is concluded that B lymphocytes or their products play an essential role in hot protection against MSV-induced tumors. (Author abstract) (29 Refs)

86. NATURAL CYTOTOXICITY AGAINST CHEMICALLY INDUCED NEUROGENIC RAT TUMORS.

De Bernardo E
Div. Endocrinology, Mount Sinai Hosp. Sch. Medicine, Fifth Ave. at 100th St., New York, NY, 10029
Exp Cell Biol; 50(1):39-55 1982

The 51Cr cytotoxicity assay was modified for ethylnitrosourea (ENU) and methylnitrosourea (MNU) induced rat neurogenic tumor cell lines. Investigations on 'immune' lymphoid cytotoxicity showed little cytotoxicity above normal. Alteration in the level of lymphocytotoxicity was seen immediately after injection of a highly immunogenic tumor (EA-528). Natural cytotoxicity (NC) was present against all neurogenic tumor cell lines tested and xenogenic cell lines. The level of NC activity was dependent on age, specific tumor cell line and could be increased by isolating the nylon wool non-adherent 'T' cell population. Allogeneic WFu rat lymphocytes were tested for NC activity in vitro against CDF tumor cells. NC activity has potential use against these tumors in vivo. (Author abstract) (40 Refs)

87. INTERACTION OF DIETARY FAT AND THE THYMUS IN THE INDUCTION OF MAMMARY TUMORS BY 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Wagner DA, Naylor PH, Kim U, Shea W, Ip C, Ip MM
(c/o M. Ip) Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Res; 42(4):1266-1273 1982

The interaction of dietary fat and the thymus in the induction of mammary tumors by dimethylbenz(a)anthracene has been examined in female Sprague-Dawley rats. In these experiments, rats fed diets of 0.5% (low fat), 5% (normal fat), or 20% (high fat) corn oil from weaning (21 days of age) were thymectomized or sham thymectomized at 35 days of age and were given 5 mg of dimethylbenz(a)anthracene at 55 days of age. Thymectomy exerted a protective effect in rats fed low and normal fat diets, and this was not reversed by Thymosin Fraction V. In high fat-fed rats, tumorigenesis was increased compared to the low fat groups, and in addition, the protective effect of thymectomy was absent. This differential effect of thymectomy could not be explained on the basis of changes in prolactin concentration, since prolactin levels were decreased in all dietary groups. Neither diet nor thymectomy affected corticosterone levels or the estrus cycle of mature rats. Peripheral blood lymphocytes were, however, decreased by both thymectomy and increasing the fat content of the diet. It is hypothesized that the promoting effect of dietary fat on dimethylbenz(a)anthracene-induced mammary tumorigenesis is mediated via the immune system, although a role for the endocrine system still cannot be ruled out. (Author abstract) (66 Refs)

88. XENOGENEIC CELLULAR IMMUNE RESPONSES AND THE CONTROL OF MICROSCOPIC TUMOR: A MODEL.

Smith TJ, Sugarbaker PH
Tufts-New England Medical Center, Boston, MA, 02111
Oncology; 39(2):93-100 1982

Regimens for the generation of a highly cytotoxic xenogeneic response, the mecha nism of this response, and its effect on tumor cells were investigated in a rat antimouse tumor system. Fischer 344 rats were immunized with EL-4 lymphoma and the ability of the sensitized rat lymphocytes to suppress the local growth of four different C57BL/6 tumors was evaluated. Optimal sensitization of the rat was achieved using large numbers of viable tumor cells in a primary intraperitoneal immunization. Highly cytotoxic effector cells generated in this xenogeneic setting significantly suppressed the local growth of appropriate tumor targets. Rat T cells appeared to be the sole effector and their effect was abrogated by anti-rat immune responses in the host mouse. This rat anti-EL-4 model will allow further investigation into xenogeneic antitumor responses and their possible role in local immunotherapy. (Author abstract) (23 Refs)

89. THE EFFECT OF THE HOLMBERG CYTOTOXIC TUMORAL FACTOR ON SPLENIC LYMPHOCYTES IN GUERIN TUMOR-BEARING RATS.

Dumitrescu R, Popp I, Tugearu
Institutul oncologic, Bucharest, Romania
Rev Chir [Oncol]; 20(2):105-111 1981

Falcon dish cultures and the Marbrook double chamber technique were used to investigate the effect of the Holmberg cytotoxic tumoral factor on splenic lymphocytes of rats bearing small (0.5-0.7 cm in diameter) and large (greater than 4 cm) Guerin tumors. In low dilutions, the factor had a general cytotoxic effect on lymphocytes, while in high dilutions, it blocked cytotoxic lymphocytes. Suppressor lymphocytes were less sensitive to the factor than were macrophages of animals with small tumors. (26 Refs) (In RUM)

90. THE EKER RENAL TUMOR RAT. GENERAL IMMUNE STATUS IN RELATION TO A VARYING TUMOR BURDEN.

Waynforth HB, Roe GM
Courtauld Inst. Biochemistry, The Middlesex Hosp. Medical Sch., London W1P 7PN, England
Neoplasma; 28(6):697-703 1981

Evidence was obtained that the response of blood lymphocytes to phytohemagglutinin was reduced in some but not all rats with massive hereditary renal tumors (greater than 50 mm mean diameter). Erythrocyte-antibody sensitized, complement dependent (EAC) rosette formation by sensitized spleen cells was also depressed in these animals, but plaque forming cell activity was essentially normal. Lesser tumor growth was associated with general cell-mediated and humoral immune responses which were within the range found for non-tumor-bearing syngeneic rats. (Author abstract) (19 Refs)

91. STUDY OF CELL-MEDIATED IMMUNITY IN B77 TUMOR BEARING RATS BY 51CHROMIUM RELEASE ASSAY.

Kalafut F, Novotna L, Valentova N
Cancer Res. Inst., Slovak Acad. Sciences, 812 32 Bratislava, Czechoslovakia
Neoplasma; 28(6):689-695 1981

Cell immunity was followed in Lewis rats with transplanted syngeneic B77 tumors, by means of the cytotoxic 51chromium release test. Lymphocytes from peripheral blood, or from regional lym ph nodes of tumor bearing animals, cocultured for 24 hr with target B77 cells had an enhanced cytotoxic effect on target cells in comparison with lymphocytes of control donors. This effect of the lymphocytes still increased during 48 hr of coculture. (Author abstract) (19 Refs)

92. TUMOR-HOST CELL INTERACTIONS IN RATS BEARING SHAY CHLOROMA - ULTRASTRUCTURAL OBSERVATIONS IN ANIMALS RECEIVING SPECIFIC AND NONSPECIFIC CANCER IMMUNOTHERAPY.

Syrjanen KJ, Soimakallio S
Dept. Pathology, Univ. Kuopio, P.O. Box 138, SF - 70101 Kuopio 10, Finland
Exp Pathol; 20(3):135-145 1981

Tumors of the rats bearing Shay chloroma treated with specific (polymerized tumor particles) and nonspecific (PPD tuberculin) cancer immunotherapy were assessed on electron microscopy with special emphasis on the interactions between the host's effector cells and the tumor targets. Attempt was made to cast light on the differences previously found in the effects of these two immunotherapy models on this particular tumor. Lymphocytes were found apposited to the tumor cells in all animals. but the nature of this contact varied from intimate in series B and C (animals receiving PPD) to extremely loose in series A (specific mode of therapy instituted). The same was true with the cells of the MPS (mononuclear phagocyte system), which sometimes seemed to wrap the tumor cells by their slender cytoplasmic processes. A prominent hypertrophy and orientation of the Golgi complex of a small lymphocyte, recently shown to be characteristic of cytolytic T-cells in vitro, was visualized in one case of series C. The observations were interpreted to lend support to the idea that blocking activity due to the polymerized strong tumor antigens could be responsible for the adverse effects of the active specific cancer immunotherapy in this particular system. (Author abstract) (41 Refs)

93. THE NATURAL KILLER SYSTEM IN THE RAT: THE RELATIONSHIP BETWEEN NATURAL AND IMMUNE CELL-MEDIATED LYSIS OF FIBROBLAST TARGETS.

Lindsay VJ, Allardyce RA
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Immunology; 45(3):423-430 1982

Natural killer (NK) cell cytotoxic activity is thought to operate as an early defense system before the expression of specific cytotoxic immune effectors. Apart from this temporal relationship it is likely that other mechanisms exist to regulate these two forms of host defense and their relationship to one another. Present studies firstly substantiate evidence that normal and immune effector cells represent different cell types even though they share many functional characteristics in vitro. Normal effector cells (NEC) cytotoxic for normal dermal-derived fibroblasts in vitro were present in rats 3-36 wk old, were tissue-dependent (with low levels in lymph nodes and thymus, unrelated to cellular suppression), were nylon wool and glass non-adherent and sensitive to 400 rad of x-irradiation in vitro. Secondly, discrimination between normal and immune cell-mediated cytotoxicity by factor(s) present in normal rat serum allowed various aspects of their in vitro and in vivo relationship to be examined. These studies suggested that the expression of NEC cytotoxicity was temporally related to the in vivo generation of immune cytotoxic effector cells. (Author abstract) (21 Refs)

94. IMMUNOLOGIC ASPECTS OF THE PROSTATE.

Lubaroff DM, Reynolds CW, Canfield L, McElligott D, Feldbush T
Dept. Urology, Univ. Iowa, Iowa City, IA, 52242
Prostate; 2(3):233-248 1981

Present knowledge of tumor immunology is reviewed, and recent research results using the Dunning R3327 tumor of the Copenhagen rat as an immunologic model of prostatic adenocarcinoma and continuing work, are described. The R3327 tumor, a well-differentiated adenocarcinoma which will grow into the sc space of the flank or within the prostate is described, and its histological appearance is shown. Earlier results included cryodestruction of the primary R3327 tumor by trocar probe procedure and demonstration of tumor-specific antigens and production of immune responses to them in xenogeneic, allogeneic, and syngeneic immunizations. Cell-mediated responses have been successfully demonstrated, including a nonspecific or natural killer activity in lymph nodes, spleen, and peripheral blood. Cryosurgery BCG have been demonstrated to induce a tumor-protective immune response in the R3327 system. Problems associated with immunotherapy are reviewed, and studies demonstrating reduced immunocompetence in patients with prostatic cancer or benign prostatic disease compared to normal individuals are described. (26 Refs)

95. SPECTRUM OF TUMORIGENIC PHENOTYPES AMONG ADENOVIRUS 2-, ADENOVIRUS 12-, AND SIMIAN VIRUS 40-TRANSFORMED SYRIAN HAMSTER CELLS DEFINED BY HOST CELLULAR IMMUNE-TUMOR CELL INTERACTIONS.

Lewis AM, Cook JL
Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Cancer Res; 42(3):939-944 1982

The tumor-inducing capacities of adenovirus Type 2-, adenovirus Type 12-, and SV40-transformed LSH hamster embryo cells define a spectrum of four distinct tumorigenic phenotypes: Type I, nononcogenic for newborn hamsters but oncogenic for nude mice; Type II, oncogenic for new born hamsters but nononcogenic in syngeneic adults; Type III, oncogenic for both newborns and syngeneic adults; and Type IV, almost equally oncogenic for syngeneic and allogeneic adult hamsters. Modulation of the cellular immune response of the recipient hamster by immunosuppression or by alloimmunization alters tumor susceptibility, suggesting that dynamic transformed cell-host cellular immune interactions determine the tumorigenic phenotype of a transformed cell line. There is no correlation between the immunogenicities of the transformed cell lines tested and their tumor-inducing capacities. However, a strong correlation exists between the ability of transformed hamster embryo cells expressing Phenotype IV to produce tumors in allogeneic CB hamsters and their resistance to cytolysis in vitro by activated macrophages. These data suggest that, in addition to transformation, DNA viruses may convey specific tumorigenic phenotypes to the cells that they infect by inducing cellular traits that determine the inherent susceptibility or resistance of a cell to host cell-mediated immune destruction. (Author abstract) (29 Refs)

96. SELECTIVE EFFECT OF FELINE LEUKAEMIA VIRUS ON EARLY ERYTHROID PRECURSORS.

Onions D, Jarrett O, Testa N, Frassoni F, Toth S

Dept. Veterinary Pathology, Univ. Glasgow, Bearsden Road, Glasgow G61 1QH, Scotland

Nature; 296(5853):156-158 1982

In a survey of feline leukemia virus (FeLV) subgroups in naturally infected cats, FeLV-C was not observed in 98 clinically normal cats but was found in 9/32 anemic cats. Subgroup C viruses from three of these anemic cats were biologically cloned and used to infect neonatal kittens. Each isolate produced a pure red cell hypoplasia (RCH), the pathology of which resembled that previously described for FeLV-C/Sarma. To determine the effect of subgroup C viruses on hematopoietic precursor cells, 3.5 x 10(5) focus-inducing units of FeLV-C/Sarma were inoculated ip within 24 hr of birth into specific pathogen-free, randomly bred cats. Control and infected cats were bled weekly to determine their blood constituents and virus status. FeLV-C/Sarma infected cats showed a rapid depletion of early erythroid precursors (burst-forming units-erythroid; BFU-E) while the proportion of the myeloid precursor (granulocyte-macrophage colony-forming cells; GM-CFC) in the bone marrow remained normal. While the mechanism of FeLV-C-induced depletion of BFU-E is unknown, any hypothesis to explain the above findings must account for the remarkable selective effect of FeLV-C in producing RCH with normal levels of GM-CFC and circulating leukocytes. (25 Refs)

97. ROLE OF THYMUS-DEPENDENT IMMUNE SYSTEM IN HVT PROTECTION AGAINST MAREK'S DISEASE.

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Dept. Veterinary Pathology, Coll. Veterinary Sciences, Haryana Agricultural Univ., Hissar--125 004 (Haryana), India

Avian Dis; 26(1):7-13 1982

The immunologic mechanism of protection against Marek's disease (MD) provided by vaccination with herpesvirus of turkeys (HVT) was investigated. T-cell deficiency (TX) was induced in 54 female chicks by thymectomy and antithymus serum (0.75 ml x2, sc). B-cell deficiency (BX) was induced in 50 chickens by cyclophosphamide (4 mg/day x4, ip) and antibursal serum (0.75 ml x2, sc). Normal and immunodeficient birds were vaccinated with lyophilized vaccine containing live cell-free HVT (2,000 plaque-forming units, sc) at 11 days of age and challenged with MD virus (3,148 plaque-forming units) several weeks later. Immunocompetent and BX birds that had been vaccinated had no mortality or gross lesions of MD following challenge, whereas similarly treated TX birds had a high incidence of MD. Immunocompetent and TX birds that had not been vaccinated developed severe MD lesions following challenge, whereas similarly treated BX birds developed no gross MD lesions. Results indicate that T cells play a major role in HVT protection against MD. (14 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

98. EFFECT OF A MONOCLONAL ANTI-LARGE GRANULAR LYMPHOCYTE ANTIBODY ON THE HUMAN NK ACTIVITY.

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J Immunol; 128(3):1097-1101 1982

A monoclonal hybridoma antibody of IgGIa subclass was produced by fusing NS-1 myeloma cells with spleen cells of a mouse immunized with human LGL cells. This hybridoma antibody, termed NK-8, was reactive by indirect immunofluorescence with 33% of peripheral blood LGL cells and 70% of LGL forming conjugates with K-562 cells. Monocytes, granulocytes, and other lymphocytes were nonreactive. In iodinated protein A binding assays NK-8 was nonreactive with all kinds of leukemia and lymphoma lines tested and showed activity only against LGL cells. NK-8 inhibited the LGL-mediated cytotoxicity against K-562 cells by 50 to 60% without complement and inhibited the K-562 induced interferon production from the LGL population. However, the spontaneous cytotoxicity against human skin fibroblasts was augmented if the effector cells were pretreated with NK-8. (Author abstract) (17 Refs)

99. INHIBITION OF MOUSE NATURAL KILLER ACTIVITY BY CYCLOSPORIN A.

Yanagihara RH, Adler WH

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Immunology; 45(2):325-332 1982

Cyclosporin A (CSA), administered in vivo or in vitro, inhibited the spontaneous cytotoxicity of C57BL/6 and NZB/WF1 mouse spleen cells against YAC and K562 target cells in a 4 hr 51Cr release assay. Inhibition of natural killing (NK) by CSA occurred rapidly, was dose-dependent, and did not require the presence of T cells, B cells or macrophages. CSA depressed NK activity by direct interaction with NK cells. There was no evidence that inhibition of NK by CSA was mediated through suppressor cells. (Author abstract) (26 Refs)

100. TRIMETHOPRIM-INDUCED AUGMENTATION OF HUMAN NATURAL KILLER ACTIVITY IN VITRO.

Matheson DS, Wilson RW, Green B

Faculty Medicine, Dept. Pediatrics, Univ. Calgary, Health Science Centre Room 1875, Calgary, Alberta T2N 4N1, Canada

Immunopharmacology; 4(1):73-77 1982

Effects of trimethoprim-sulfamethoxazole (TMP-SMX) on the natural killer (NK) activity of peripheral blood mononuclear cells from normal humans were studied in vitro. TMP-SMX consistently caused an augmentation in NK activity, and did not alter the background lysis of the target cells in the absence of effector cells. Augmentation by TMP alone essentially paralleled that of TMP-SMX, suggesting that TMP was the drug which mediated the response. (12 Refs)

101. AUTOLOGOUS MECHANISMS GENERATING NATURAL KILLER ACTIVITY WITHIN HUMAN PERIPHERAL LYMPHOCYTES DEPLETED OF NK TARGET-BINDING CELLS.

Whisler RL, Bakenhaster K, Opremcak EM

Div. Immunology, Dept. Medicine, Ohio State Univ., Columbus, OH, 43210

Cell Immunol; 66(2):342-351 1982

Human peripheral blood lymphocytes (PBL) were depleted and enriched for natural killer target-binding cells (NK-TBC) by sedimentation of MOLT 4 tumor conjugate suspensions over discontinuous gradients. NK-TBC-depleted PBL consistently demonstrated diminished NK cytolytic levels whereas the NK levels of PBL enriched for NK-TBC were at least six- to eight-fold greater. An equal ratio of NK-TBC-enriched and depleted PBL combined at the time of cytotoxicity assay demonstrated NK levels intermediate between those of TBC-enriched and depleted PBL. However, coculturing NK-TBC-enriched and depleted PBL for 18 hr resulted in levels equivalent to those of NK-TBC-enriched cells and greater than those predicted from either population cultured alone. The increased NK activity in 18-hr cocultures required protein synthesis by TBC-enriched cells but was not abrogated by anti-interferon antibodies. In other experiments both NK-TBC-depleted and -enriched populations demonstrated considerable NK activity after exposure to autologous non-T lymphocytes. Also, autologous monocytes were found to inhibit the generation of NK activity among TBC-depleted PBL exposed to autologous non-T lymphocytes. The results suggest that non-TBC PBL have the potential to develop functional NK activity and that differing autologous mechanisms might be responsible for NK generation. (Author abstract) (19 Refs)

102. INHIBITION OF HUMAN NATURAL KILLER CELL ACTIVITY BY CYTOPHILIC IMMUNOGLOBULIN G.

Sulica A, Gherman M, Galatiuc C, Manciulea M, Herberman RB

Victor Babes Inst., Bucharest, Romania

J Immunol; 128(3):1031-1036 1982

The natural killer (NK) cell activity of human peripheral blood mononuclear cells (PBL) was found to be increased after incubation at 37 C for 2 hr. The observed increase was shown to be associated with release from inhibition by human serum factors, because incubation in autologous serum interfered with augmentation. The serum-mediated effect appeared attributable to the degree of binding of labile IgG to PBL and could be reduced by selective depletion of IgG from the serum. Human monomeric IgG was found to efficiently inhibit the culture-induced augmentation of NK activity; the inhibitory IgG had properties consistent with those described for cytophilic IgG and was mediated through the Fc region of IgG. The inhibition by monomeric IgG occurred at 0 C as well as at 37 C and this could be induced even after culture-induced augmentation of NK activity. Thus, binding of monomeric IgG to human PBL appears to reversibly inhibit their NK activity. These results provide evidence for a novel mechanism for negative regulation of NK activity. (Author abstract) (45 Refs)

103. STUDIES ON NATURAL KILLER (NK) CELLS. III. THE EFFECTS OF IN VITRO CULTURE ON SPONTANEOUS CYTOTOXICITY OF MURINE SPLEEN CELLS.

Bartlett SP, Burton RC
Transplantation Unit, Harvard Medical Sch. at Massachusetts General Hosp., Boston, MA, 02114
J Immunol; 128(3):1070-1075 1982

In vitro culture of normal lymphohemopoietic cells is a complex event leading to the generation of a diverse group of effector cells. When murine spleen cells are cultured by themselves in fetal calf serum containing medium for up to 9 days, at least three distinct subpopulations of cytotoxic effectors can be distinguished on the basis of tumor target cell preference and expression of cell surface alloantigens. Fresh spleen cell suspensions contain two distinct NK cell types: NK-1.2 NKA cells, which preferentially lyse lymphoma targets, and NK-1.2-NKB cells, which lyse nonlymphoma, mainly solid tumor targets. These NK cells account for all the cytolytic activity on day 0 of culture. NK-1.2 NKA cells are very labile, and greater than or equal to 80% of their activity is lost within 48 hr of culture. By contrast, the activity of NKB cells increases in culture, up to four-fold by day 6, and solid tumor target cells resistant to lysis by fresh spleen cells now become susceptible. In addition, an NK-1.2-, H-2, Thy-1.2, Ly-1.2, Ly-2.2 cytotoxic effector cell arises in culture from, or is dependent upon the presence of, NK-1.2-, Thy-1.2 cells. This spontaneously arising 'Tc' has a peak of activity between day 3 and 6 of culture, and kills a variety of lymphohemopoietic tumor cell types. (Author abstract) (35 Refs)

104. SR-INDUCED INHIBITION OF HUMAN NATURAL KILLER (NK) CELL-MEDIATED CYTOTOXICITY.

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Dept. Patholgoy, Albert Einstein Coll. Medicine, Bronx, NY, 10461
J Immunol; 128(3):1236-1240 1982

The cell believed to be responsible for human spontaneous cytotoxicity or natural killing (NK) has been described recently as a large granular lymphocyte (LGL). Because the intracytoplasmic granules of LGL appear to be peculiar to the subpopulation of mononuclear cells containing NK effectors, we have investigated their possible requirement in the cytolytic process. Experiments reported here show that SR, a cation known to cause degranulation of granulocytes, caused a dose- and time-dependent inhibition of the NK activity of human peripheral blood mononuclear cells. A single-cell NK assay showed that the number of cytotoxic cells was not significantly reduced, but that Sr inhibited NK by preventing individual effector cells from engaging in multiple lethal hits. Moreover, the inhibition of NK appeared to be reversible; culture in vitro of Sr-treated PBMC resulted in the eventual return of cytolytic activity in these cells. Augmentation of NK by interferon (IFN) was similarly blocked by SR. In addition, Sr also inhibited the NK activity of IFN-prestimulated effector cells and, as before, NK function returned during subsequent culture. These results indicated that the return of NK function after Sr treatment was the result of reactivation of cytotoxic cells rather than recruitment of new effectors. We have shown in other studies that Sr degranulates LGL, and the data presented here provide support for the hypothesis that the intracytoplasmic granules of LGL are required for NK-mediated cytotoxicity. (Author abstract) (21 Refs)

105. IN VITRO ACTIVITY OF NK-CELLS FROM C57BL/6 MICE IRRADIATED AND IMMUNOSTIMULATED BY CORYNEBACTERIUM PARVUM.

Badea E, Corneci I, Rozescu B
Oncological Inst. Bucharest, Bucharest, Romania
Rev Chir [Oncol]; 20(3):185-191 1981

The in vitro activity of natural killer cells (NK) was studied after irradiation and/or stimulation of the donor animal with Corynebacterium parvum. Adult male and female C57BL/6 mice were exposed to 500 rad x-rays. Various groups received 2.0-2.5 mg dried C parvum injected ip 30, 14, 7, 5, or 3 days or 1 hr before irradiation or 1 hr or 3 days after irradiation. Mice were killed 9 days after irradiation and splenocytes and peripheral blood cells were obtained. NK activity was analyzed against syngeneic (Lewis tumor growing in C57BL/6 mice), allogeneic (Ehrlich ascites growing in A strain mice), and xenogeneic (B1R ascites and MC fibrosarcoma growing in R strain rats) tumor cells. An av spontaneous NK cytotoxicity of 27% was observed. Irradiation reduced NK activity to 21%, indicating that NK are relatively radioresistant. NK activity did not vary significantly with the sex of the donor or with the type of target cell. C parvum inoculation stimulated macrophage production. However, removal of macrophages did not affect NK activity, indicating that macrophages do not affect the promotion phase of NK. C parvum inoculation produced the greatest NK activity 4 days after inoculation. NK activity declined after day 4 but remained elevated 6-12 days longer. (22 Refs)

106. INDUCTION OF NATURAL KILLER CELLS DURING MURINE INFLUENZA VIRUS INFECTION.

Leung KN, Ada GL
Dept. Microbiology, John Curtin Sch. Medical Res., Australian Natl. Univ., Canberra, A.C.T. 2601, Australia
Immunobiology; 160(3/4):352-366 1981

Cells which are cytotoxic for both virus-infected and uninfected target cells can be recovered from the spleens of mice injected with either infectious or non-infectious influenza A virus. Peak activity occurs at 1-2 days and decreases to low levels by day 6. The effector cells are insensitive to anti-Thy 1 antibody and complement treatment, are not H-2 restricted, do not adhere to plastic and are unaffected by silica or carrageenan. In this sense and in the pattern of susceptibility to lysis of a variety of cultured cell lines, these effector cells have the properties of natural killer (NK) cells and are referred to as such. They are present to an increased level of activity in nude (nu/nu) mice and to a low level of activity in beige (bg/bg) mice, but upon injection of virus there is a significant increase in activity in both hosts. Such cells were also recovered from the lungs of mice infected intranasally with a lethal or sublethal dose of virus. In the former case, maximum activity was reached 2 days post infection and the activity remained high until death; in the latter case, peak activity was reached 4 days after virus inoculation and by day 11 the activity had decreased to pre-infection levels. After intranasal inoculation of influenza virus, both beige mice and their heterozygous littermates contained similar levels of infectious virus in their lungs. However, this result does not eliminate the possibility that these cells may help to limit virus infection. (Author abstract) (38 Refs)

107. EFFECTS OF A TUMOR PROMOTER, 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (TPA) ON HUMAN PERIPHERAL BLOOD LYMPHOCYTES: INDUCTION OF SUPPRESSOR T CELLS AND REDUCTION OF NATURAL KILLING (NK) AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC).

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Mie Med J; 31(1):37-52 1981

Effects of the tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA) were studied in human peripheral blood lymphocytes (PBL) from normal healthy adult donors. Cell suspensions of T cells, B cells, and monocytes were exposed to TPA, concanavalin A (ConA), phytohemagglutinin (PHAP), and pokeweed mitogen (PWM) in various combinations and concentrations. Optimum stimulation of PBL was obtained 96 hr after addition of 10(-7) M TPA. TPA produced significant stimulation of PBL at concentrations of 10(-8)-10(-6) M with peak responses occurring after 3-5 days. TPA nonselectively stimulated T cells and B cells. PHAP and ConA stimulated predominantly T cells. In mixed lymphocyte reactions pretreatment of either the responder T cells or stimulating allogeneic cells with TPA inhibited DNA synthesis. Cells activated by TPA (or supernatant from these cells) suppressed proliferative response by autologous T and B cells to allogeneic cells or mitogens. TPA induced formation of T cells bearing IgG-Fc receptors and T cells forming autologous erythrocyte rosettes. TPA evidently induces suppressor T cells or T cell subsets required for suppressor activity. TPA actively suppressed the activity of natural killer (NK) cells and killer cells effecting antibody-dependent cellular cytotoxicity (ADCC). TPA should be useful for studies of suppressor mechanisms, NK activity, and ADCC. (64 Refs)

108. STIMULATION OF NATURAL KILLER CELL ACTIVITY AND INHIBITION OF PROLIFERATION OF VARIOUS LEUKEMIC CELLS BY PURIFIED HUMAN LEUKOCYTE INTERFERON SUBTYPES.

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Genentech, Inc., South San Francisco, CA, 94080
Cancer Res; 42(4):1312-1316 1982

One of several human leukocyte interferon subtypes A (LeIF-A), obtained in purified form from a gene cloned in Escherichia coli, stimulated human peripheral blood natural killer cell activity, whereas another human leukocyte interferon subtype D (LeIF-D) had no effect with the use of K562 as target cells. With Daudi as target cells, both LeIF-A and LeIF-D stimulated natural killer cell activity. A hybrid human leukocyte interferon, NH2-terminal 61 amino acids and COOH-terminal 104 residues of LeIF-A and LeIF-D, respectively (LeIF-AD) showed greater stimulation than did LeIF-A, but the stimulation did not exceed that of natural buffy coat interferon. A mixture of equal antiviral units of LeIF-A and LeIF-D was no more effective than was LeIF-A alone. The cloned interferon subtypes showed differential effects on the proliferation of three human leukemic cell lines: Daudi (B-cell lymphoblastoid leukemia); BALL 1 (B-cell acute lymphoblastic leukemia); CCRF-HSB-2 (T-cell acute lymphoblastic leukemia). Growth of Daudi cells was generally most sensitive to all the interferons tested, LeIF-A, -D, -AD, and a buffy coat preparation; no viable cells remained after 120 hr exposure to 1,000-unit/ml doses of the interferons. BALL 1 was relatively resistant to the interferon subtypes tested including LeIF-AD, but this cell line was very sensitive to a preparation of natural buffy coat interferon. CCRF-HSB-2 showed some sensitivity to all the interferons with greatest sensitivity to LeIF-A (10% of the viable cells were detected after 1,000 units/ml exposure for 120 hr). In contrast to the leukemic cell lines tested, human amnion cells (WISH) and the human erythroid leukemia, K562, were resistant to the antiproliferative activity of the interferons. (Author abstract) (23 Refs)

109. EFFECT OF CYTARABINE ON CYTOTOXIC T-CELL DEVELOPMENT.

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Donald S. Walker Lab., Sloan-Kettering Inst. Cancer Res., 145 Boston Post Road, Rye, NY, 10580
Cancer Treat Rep; 66(3):535-540 1982

Administration of repeated high doses of cytarabine to normal C57BL/6 mice causes a depression of in vitro cytotoxic T-cell development against allogeneic tumor cells. This low cytotoxic T-cell response occurs in the absence of a reduction in cytotoxic T-cell precursor cells. The low cytotoxic response can be restored to normal levels when a source of helper factor is added to the culture system. (Author abstract) (32 Refs)

110. EFFECT OF UREMIC SERUM ON E-ROSETTE FORMATION OF NORMAL LYMPHOCYTES MODULATED BY LEVAMISOLE.

Modai D, Peller S, Weissgarten J, Shaked U, Kaufman S
Dept. Medicine A, Nephrology Unit, Assaf Harofeh Hosp., 61027 Zerifin, Israel
Isr J Med Sci; 17(12):1115-1118 1981

The number of E-rosette forming cells of lymphocytes from healthy subjects was determined under various experimental conditions. Sera from 16 chronic hemodialysis patients were incubated with lymphocytes from 16 matched normal subjects. The effect of levamisole on this combination was studied. Uremic serum markedly inhibited E-rosette formation of normal lymphocytes. Pretreatment with levamisole completely prevented this effect, whereas levamisole treatment following incubation with uremic serum resulted in a partial correction of the E-rosette formation. The hypothesis best fitting these results is that a factor present in uremic serum blocks sheep red cell receptors on normal lymphocytes; levamisole, having a greater affinity for these receptors, prevents or partially corrects the effect of the blockade. (Author abstract) (20 Refs)

111. DIFFERENTIAL VARIATIONS OF SENSITIVITIES OF TNP-MODIFIED LYMPHOMA CELLS TO LYSIS BY CYTOTOXIC LYMPHOCYTES AND BY ANTIBODIES.

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Immunol Lett; 4(2):107-111 1982

The susceptibility of a well-defined target cell line, towards both cell-mediated lysis and antibody plus complement lysis was compared under fully parallel experimental situations. Cultured RDM4 lymphoma cells were modified with 1 milliM trinitrobenzene sulfonate (TNBS) and assayed for lysis by either in vitro generated cytotoxic T-lymphocytes (CTL) or complement-mediated humoral immunity. The lytic effect of CTL was always greater in the 'youngest' cells (those in exponential growth, as shown by marked incorporation of (3H)thymidine [TdR]) than in cultures in which cells were in the resting phase. In some experiments, RDM4 cells were harvested after 1-4 days of culture and labeled with (3H)TdR or (14C)TNBS. The oldest cells incorporated less (3H)TdR than the youngest cells, but bound more (14C)TNBS to their surface. It is concluded that the efficiency of the CTL on the hapten (trinitrophenyl [TNP])-modified cell is is not proportional to the density of TNP-groups on the targets, and that CTL on the one hand, and complement-mediated humoral immunity on the other hand, must have different cell surface requirements to be able to lyse the target cells. (16 Refs)

112. LYMPHOCYTIC MEDIATORS.

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Institutul Oncologic, Cluj-Napoca, Romania
Rev Chir [Oncol]; 20(2):81-88 1981

Studies on lymphocytic mediators (transfer factor, lymphocyte transformation factor, chemotactic factor, migration inhibition factor, macrophage disappearance factor, macrophage activating factor, lymphotoxins, clonal inhibition factor, interferon, skin reactivity factor, and lymph node permeability factor) are reviewed. The experimental and clinical applications of these factors include tumor immunological studies and immunotherapy. (27 Refs) (In RUM)

113. CYCLOSPORIN A ABROGATES PROLIFERATION OF T CELLS AND GENERATION OF SUPPRESSOR AND CYTOTOXIC T-CELL FUNCTION INDUCED BY EPSTEIN-BARR VIRUS.

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Immunobiology; 160(3/4):321-329 1981

Cyclosporin A (CYA) promotes the outgrowth in vitro of Epstein-Barr-virus (EBV)-infected cells of immune donors. In the present study, the effects of CYA on the T-cell responses developed in an in-vitro EBV infection were studied. Cyclosporin A, by acting on the responder cells and not on stimulator cells, strongly inhibited the proliferation of T cells normally induced by EBV-infected autologous cells. Moreover, T cells from cultures not exposed to CYA exerted suppression on both alloantigen-induced DNA synthesis and PWM-stimulated immunoglobulin production of autologous peripheral blood mononuclear cells. In contrast, T cells from cultures treated with CYA exhibited significantly less or no suppressor activity as determined in both indicator systems. Finally, CYA abrogated the generation of cytotoxic T cells against EBV-infected autologous cells, whereas non-CYA-treated T cells killed the virus-transformed target cells. Both suppressor and cytotoxic T-cell functions are known to play an essential role in the control of EBV infection by limiting the continuous growth of the virus-infected cells. These results, therefore, strongly suggest that Cyclosporin A promotes the outgrowth of EBV-infected cells by abrogating the T-cell responses to the Epstein-Barr virus. (Author abstract) (23 Refs)

114. AN ACUTE LYMPHOBLASTIC LEUKEMIA WHICH PRODUCES HUMAN T CELL GROWTH FACTOR.

Anderson DW, Hayward A, Jones C
Eleanor Roosevelt Inst. Cancer Res., Univ. Colorado Health Sciences Center, Denver, CO, 80262
Immunol Commun; 10(8):697-706 1981

We report the production of T cell growth factor activity by a PHA stimulated acute lymphoblastic leukemia cell line designated HSB-2. Factor production was enhanced by the addition of phorbol myristate acetate to the cultures. The growth factor will enhance the proliferation of PHA stimulated thymocytes and sustain the proliferation of growth-factor dependent human T cell blasts. The characteristics of the cell line are described. (Author abstract) (18 Refs)

115. INDUCTION OF PROLIFERATION AND IG PRODUCTION IN HUMAN B LEUKEMIC CELLS BY ANTI-IMMUNOGLOBULINS AND T CELL FACTORS.

Yoshizaki K, Nakagawa T, Kaieda T, Muraguchi A Yamamura Y, Kishimoto T
Third Dept. Medicine, Osaka Univ. Medical Sch., Fukushima-ku, Osaka 553, Japan
J Immunol; 128(3):1296-1301 1982

The proliferation and differentiation of human leukemic B cells (B-CLL cells) with anti-Ig and T cell-derived helper factors are described. Stimulation of B-CLL cells with anti-Ig and T helper factors could induce proliferation as well as differentiation into IgM- and IgG-producing cells. Neither anti-Ig nor T helper factors alone could induce any proliferation and/or differentiation of B-CLL cells. Not only whole molecules of anti-Ig but also F(ab')2 fragments could induce proliferation and differentiation of B-CLL cells in the presence of T helper factors, but monovalent Fab' fragments were not effective. Induction of both IgM and IgG with the same idiotype was confirmed by immunofluorescent and SDS-PAGE analysis. By employing an IL 2-dependent cytotoxic T cell line and a TRF-responsive B cell line, T cell factors were separated into a fraction with IL 2 activity but no TRF activity and a fraction with TRF activity but no IL 2 activity by chromatofocusing. Anti-Ig and IL 2 fraction could induce proliferation of B-CLL cells, but TRF fraction was not effective for the induction of proliferation in anti-Ig-stimulated cells. For IgM and IgG production, anti-Ig and both IL 2 and TRF fractions were required. Depletion of IL 2 fraction in the first 2 days' culture inhibited Ig production, whereas the absence of TRF fraction in the first 2 days did not show any inhibitory effect on Ig production. (Author abstract) (26 Refs)

116. CELLULAR AND GENETIC RESTRICTIONS IN THE IMMUNOREGULATORY ACTIVITY OF ALPHA-FETOPROTEIN. III. ROLE OF THE MLC-STIMULATING CELL POPULATION IN ALPHA-FETOPROTEIN-INDUCED SUPPRESSION OF T CELL-MEDIATED CYTOTOXICITY.

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Dept. Pathology, Coll. Medicine, Univ. Florida, Box J-275, Gainesville, FL, 32610
J Immunol; 128(3):1134-1140 1982

Alpha-fetoprotein (AFP), a normal component of fetal and newborn sera, exerts selective suppressive effects on various functions of thymus-derived (T) lymphocytes, including the T cell-mediated cytotoxic reaction. In the present study, AFP-induced suppression of the T cell-mediated allogeneic response was examined to define more precisely the mechanism by which AFP acts. Data presented indicate that AFP elicits its effect within the first 24 to 36 hr of culture. However, AFP apparently has no direct effect on T lymphocytes. T cells incubated in the presence of AFP retain full capacity to respond in MLC and CML. In contrast, AFP induces major changes in the functional status of monocyte-enriched, MLC-stimulating cell populations. This monocyte-enriched population, after pretreatment with AFP, possesses strong stimulating capacity for the T suppressor cell limb of the immune response, while at the same time, suppresses the activity leading to the normal generation of cytotoxic T lymphocytes. These data correlate with the immune activity present in the newborn mouse. (Author abstract) (29 Refs)

117. THE PURIFICATION AND PROPERTIES OF HUMAN T CELL GROWTH FACTOR.

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J Immunol; 128(3):1122-1127 1982

Human T cell growth factor (TCGF) has been purified more than 800-fold from serum-free lymphocyte conditioned media by utilizing ion exchange chromatography with DEAE-Sepharose, gel filtration with Ultrogel AcA54, and preparative SDS-polyacrylamide gel electrophoresis. This mitogenic protein, which is released by T cells into the incubating media after exposure to a lectin (PHA), has a mw of 13,000 as determined by SDS-PAGE and 20,000 to 25,000 on gel filtration and has an isoelectric point of 6.8. The material extracted from acrylamide gels is a single band (or 2 nearly superimposed bands) when rerun on analytical SDS gels. Partially purified material is unstable even at-70 C and requires the addition of bovine serum albumin or polyethylene glycol to maintain biologic activity. It is sensitive to proteolytic digestion but resistant to nucleases and thiol-reducing agents such as dithiothreitol. Human TCGF can be reversibly denatured with urea or SDS. Material extracted from acrylamide gels has been shown to sustain T lymphoblasts in tissue culture. In contrast to lectins, certain antigens, and crude lymphocyte conditioned media, purified TCGF does not initiate lymphocyte blastogenesis but is a highly selective mitogen for T cells previously activated by exposure to lectins or antigens. (Author abstract) (29 Refs)

118. ANTIGEN-NONSPECIFIC HELPER FACTORS IN THE ANTIBODY RESPONSE.

Farrar JJ, Hilfiker ML
Lab. Microbiology and Immunology, Natl. Inst. Dental Res., Bethesda, MD, 20205
Fed Proc; 41(2):263-268 1982

Four biochemically distinct antigen-nonspecific factors have been shown to augment the antibody response to particulate thymic-dependent antigens, ie, heterologous erythrocytes. These factors are the lymphokines colony-stimulating factor, T cell-replacing factor, and interleukin 2, as well as the monocyte product interleukin 1. The immunoenhancing role of each of these factors in the antibody response is reviewed. A description of the biochemical properties of each factor, the biochemical separation of each factor for other helper factors, the separation of certain factors using different producing cells, and a description of the culture systems used to demonstrate helper activity are included. Questions concerning the target cell specificity and hence the mechanism of action of each factor are raised. Finally, recent data from several laboratories demonstrating the synergistic interactions of the helper factors in enhancing antibody synthesis are reviewed and models of B cell activation are presented. (Author abstract) (58 Refs)

119. LYMPHOKINES: THEIR ROLE IN LYMPHOCYTE RESPONSES. PROPERTIES OF INTERLEUKIN 1.

Oppenheim JJ, Stadler BM, Siraganian RP, Mage M, Mathieson B
Lab. Microbiology and Immunology, Natl. Inst. Dental Res., NCI, NIH, Bethesda, MD, 20205
Fed Proc; 41(2):257-262 1982

Interleukin 1, or IL 1, otherwise known as lymphocyte-activating factor, is a macrophage-derived 12,000-to 15,000-dalton polypeptide. Isoelectric focusing of human IL 1 reveals three peaks at pI's of 5.2, 6.0, and 6.9, respectively. IL 1 can be depleted of lymphocyte-derived IL 2 by SP-Sephadex chromatography. IL 1 augments the mitogenic response of PNA- Lyt 1 thymocytes, and promotes thymocyte helper functions and B cell antibody production. IL 1 induces stable E rosette formation and the production of lymphokines such as T cell growth factor (IL 2) by peripheral T lymphocytes. Others have shown that IL 1 or closely related factors also stimulate hypothalamic cells to induce fever; induce in vitro fibroblast growth, prostaglandin, and collagenase production; and stimulate hepatocytes to produce acute phase proteins such as serum amyloid A. Murine epidermal cells also produce a 15,000-dalton factor that is mitogenic for thymocytes and may be similar to IL 1. We have recently hybridized spleen cells from mice sensitized with partially purified human IL 1 with a myeloma cell line. Clones have been isolated that produce supernatants that partially inhibit the thymocyte proliferative response to IL 1 but not the T cell growth factor activity of IL 2. Should these hybridoma products prove to be monoclonal anti-IL 1 antibodies, they will facilitate the further purification and characterization of IL 1. (Author abstract) (43 Refs)

120. INDUCTION OF SPECIFIC CELL-MEDIATED CYTOTOXICITY IN VITRO BY MEANS OF RNA ISOLATED FROM ALLOGRAFTED MICE.

Holan V, Lipoldova M, Zadrazil S, Hasek M
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Folia Biol (Praha); 27(6):422-426 1981

Immune RNA was prepared by sensitization of B10.A mice with allogeneic skin grafts from C57BL/10Sn mice and extraction from spleens and lymph nodes in cold phenol-chloroform-isoamyl alcoho l. The RNA extracts induced specific cell-mediated immunity in vitro in lymphocytes of normal B10.A mice, demonstrated by 3H-thymidine microcytoxicity assay in surviving cells of MC11 sarcoma induced in B10 mice or in cells of two Rous sarcoma virus-induced tumors in Wistar rats or DBA mice. The RNA immunospecific cytotoxicity persisted after deoxyribonuclease and pronase treatment but not after ribonuclease treatment, indicating that RNA activity is involved in the induction process. (16 Refs)

121. HUMAN PREALBUMIN FRACTION: EFFECTS ON CELL-MEDIATED IMMUNITY AND TUMOR REJECTION.

Leung KH, Ehrke MJ, Bercsenyi K, Mihich E
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Immunopharmacology; 4(1):55-67 1982

Effects of human prealbumin fraction on primary and secondary cell-mediated immunity in vitro, and the effects of the prealbumin fraction on tumor rejection by C57B/6J and DBA/2J normal adult female mice, were studied. The prealbumin fraction was isolated from pooled human plasma by extraction with aqueous buffer and gel filtration. Prealbumin caused a dose-dependent augmentation of responses. (26 Refs)

122. DNA REPAIR AFTER GAMMA RADIATION AND SUPEROXIDE DISMUTASE ACTIVITY IN LYMPHOCYTES FROM SUBJECTS OF FAR ADVANCED AGE.

Licastro F, Franceschi C, Chiricolo M, Battelli MG, Tabacchi P, Cenci M, Barboni F, Pallenzona D
Inst. General Pathology, Univ. Bologna, Via S. Giacomo 14, 40126 Bologna, Italy
Carcinogenesis; 3(1):45-48 1982

DNA repair after gamma radiation was studied in purified T lymphocytes from young and aged subjects. Two different assays were employed. In the first, T lymphocytes were stimulated with phytohemagglutinin (PHA) for 72 hr and then treated with hydroxyurea, irradiated with 30 K rads and pulsed with [3H]thymidine (TdR) for 4 hr. In the second, T lymphocytes were first irradiated with graded doses of gamma rays (200-800 rads) and then stimulated with PHA, cultured for 72 hr and pulsed with 3H-TdR for the last 6 hr of culture. T lymphocytes from aged subjects showed a lack of DNA repair synthesis in the first assay whereas only minor differences were found in the second assay between the two groups, ie, a certain degree of radioresistance in aged lymphocytes. Lymphocyte superoxide dismutase activity showed great individual variations in both groups and a slight increase in old subjects. (Author abstract) (44 Refs)

123. MITOGEN STIMULATION OF LYMPHOCYTES EXPOSED TO LEAD.

Blakley BR, Archer DL
Dept. Veterinary Physiological Sciences, Western Coll. Veterinary Medicine, Univ. Saskatchewan, Saskatoon, Saskatchewan S7N 0W0, Canada
Toxicol Appl Pharmacol; 62(2):183-189 1982

Effects of in vivo lead exposure on various in vitro mitogenic responses were investigated. The responses were evaluated using the T-cell mitogens concanavalin, phytohemagglutinin, and staphylococcal enterotoxin A (SEA). Escherichia coli lipopolysaccharide was used to assess B-cell responses in vitro. In vivo T-cell responses were evaluated using SEA. Results indicate that the effects of lead on the mitogen response in vitro may reflect the true functional capability of the immune system in vivo. (18 Refs)

124. EFFECTS ON ANTIBODY-PRODUCING CELLS AND PERIPHERAL BLOOD LYMPHOCYTE SUBPOPULATIONS (T- AND B-CELLS) OF P-MSY, A SUBSTANCE WITH ANTITUMOR ACTIVITY FROM BOVINE PAROTID GLAND.

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Chem Pharm Bull (Tokyo); 29(11):3298-3304 1981

The effects of the hypocalcemic protein P-MSY (extracted from bovine parotid gland) on the numbers of mouse spleen direct (IgM-producing) and indirect (IgG-producing) plaque-forming cells (PFC) against sheep erythrocytes was studied, and the influence of P-MSY and its intermediate, PAIA, on the peripheral blood lymphocyte subpopulations in guinea pigs was determined. The numbers of both direct and indirect PFC from mice receiving 1-5 ug/mouse P-MSY were approx 1.9 to 2.9-fold those of controls. A dose-level response could not be demonstrated, however. P-MSY may accelerate the ontogenic maturation of the immunolymphoid system. Injection (ip) of 80 ug of PAIA and of 10 or 20 ug P-MSY into neonatal guinea pigs resulted in elevation of T-cells relative to B-cells at 14 days of age compared to controls. The relative increase in T-cell subpopulation in peripheral blood lymphocytes following administration of P-MSY seems to result from simulation of stem cell differentiation into immunocompetent T-cells. This protein may enhance the helper function of T-cells, and hence stimulate B-cell activity. (21 Refs)

125. INDUCTION OF ANTIGEN-SPECIFIC LYMPHOCYTE UNRESPONSIVENESS IN VITRO: POSSIBLE ROLE OF DIVALENT CATIONS AND DEFECTIVE FUNCTION OF HUMAN T-CELL-ACTIVATING FACTOR (TAF).

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Cell Immunol; 66(1):152-163 1982

Antigen-stimulated blood mononuclear cells preincubated for 22 hr in vitro with Cd, but not with five other divalent metal ions, failed to elaborate leukocyte migration inhibitory factor (LIF) upon restimulation with the specific antigen. Moreover, cells challenged with antigen did not secrete LIF when pretreated with the specific antigen plus the divalent cation chelator, phenanthroline; an effect counteracted by Zn and Co. The concentration of antigen needed for induction of tolerance was the same as that required for stimulation of LIF production in the absence of the tolerogens, Cd and phenanthroline. No evidence for the involvement of suppressor cells was found. Tolerization was antigen specific, since lymphocytes pretreated with antigen plus tolerogen responded normally when challenged with an unrelated recall antigen. The lack of responsiveness could not be ascribed to generalized cell death, carry-over of the tolerogens, or exhaustive release of LIF during tolerization. Phenanthroline and Cd both inhibit the activities of carboxypeptidases as well as the monocyte/macrophage-derived T-cell-activating factor (TAF), the effect of which is exerted nonspecifically on antigen-stimulated T cells in G1. Seen in the context of a two-signal model of T-cell activation and paralysis, delivery of signal Number 1 (the antigen) without addition of the nonspecific signal Number 2 (TAF?). Results of kinetic experiments support this assumption. (Author abstract) (22 Refs)

126. EFFECT OF COLONY STIMULATING FACTOR ON MURINE MACROPHAGES. INDUCTION OF ANTITUMOR ACTIVITY.

Wing EJ, Waheed A, Shadduck RK, Nagle LS, Stephenson K
Dept. Medicine, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA, 15213
J Clin Invest; 69(2):270-276 1982

Colony stimulating factor (CSF) was assessed for its capacity to stimulate antitumor activity in macrophages. Murine peritoneal macrophages incubated with CSF for 48 hr inhibited [3H]thymidine (TdR) incorporation by P815 tumor cells to approx 20% of control values. Inhibition of CSF-stimulated macrophages was significantly greater than inhibition by unstimulated macrophages (p less than 0.001). CSF had little direct effect on the proliferation of either tumor cells or macrophages alone, indicating that the antitumor activity of CSF was mediated by macrophages. It is unlikely that impurities in the CSF preparations were responsible for the effect since CSF that had been purified to homogeneity was as active as crude preparations. Furthermore the activity of CSF on macrophages was blocked by addition of purified anti-CSF antibodies. In addition to being tumoristatic, CSF-stimulated macrophages were tumoricidal as determined by a tumor colony growth assay. Tumor cells that had been incubated with CSF-stimulated macrophages showed a significant reduction in tumor colony-forming units (p less than 0.01). Thus, in addition to its effect on hemopoietic stem cells, CSF induces certain effector functions in mature macrophages that may enhance endogenous antitumor host defenses. (Author abstract) (21 Refs)

127. EFFECT OF HUMAN RECOMBINANT INTERFERON ON CYTOTOXIC ACTIVITY OF NATURAL KILLER (NK) CELLS AND MONOCYTES.

Herberman RB, Ortaldo JR, Mantovani A, Hobbs DS, Kung HF, Pestka S
Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD, 20205
Cell Immunol; 67(1):160-167 1982

Studies have been performed on the in vitro immunologic effects of homogeneous recombinant human leukocyte interferon, IFLrA. Large granular lymphocytes, enriched for natural killer (NK) cell activity, were pretreated with IFLrA or natural interferon preparations and then tested for augmentation of NK activity and of antibody-dependent cell-mediated cytoxicity (ADCC). Monocytes were tested for cytolytic and cytostatic activity in 48-72 hr radioisotopic assays performed in the presence or absence of interferon. Treatment with IFLrA caused significant augmentation of NK, ADCC, and monocyte-mediated cytotoxic activities. Even 10 units of IFLrA induced augmentation of NK activity, and 100 units or more boosted monocyte-mediated activity. The effects in each of these assays were species-specific, with no detectable effects on the activity of mouse effector cells. These results indicate that homogeneous recombinant interferon has potent in vitro immunomodulating effects and thus provide a basis for carefully examining the in vivo effects of this protein on host defenses in forthcoming clinical trials with cancer patients. (Author abstract) (43 Refs)

128. INTERFERON-INDEPENDENT, LECTIN-INDUCED AUGMENTATION OF MURINE NATURAL KILLER CELL ACTIVITY.

Brunda MJ, Varesio L, Herberman RD, Holden HT
Lab. Immunodiagnosis, NCI, Bethesda, MD, 20205
Int J Cancer; 29(3):299-307 1982

The ability of lectins to augment natural killer (NK) cell activity was demonstrated using splenic effector cells from athymic nude mice. The addition of Helix pomatia agglutinin to the assay or pretreatment of the effector cells with lectin resulted in increased cytotoxicity against the human cell line K562, a relatively poor target for spontaneous mouse NK activity. When additional lectins were tested, NK activity was increased markedly by some lectins while others had no effect. The augmentation of cytotoxicity was dependent on the concentration of lectin added. Nylon-wool-nonadherent, nu/nu splenic effector cells mediated the lectin-induced cytotoxicity, and antiasialo GM1 plus complement abolished activity, indicating that the cells mediating the cytotoxicity were NK cells and not mature T cells, B cells or macrophages. When spleen cells from mice having different levels of NK activity were evaluated in this system, the magnitude of the lectin-induced cytotoxicity obtained correlated with the level of spontaneous NK activity and no increased cytotoxicity was found using cell populations that had low spontaneous NK activity. By testing a panel of target cells, we found that certain human, mouse and rat cell lines, which had low to moderate susceptibility to spontaneous murine NK activity, were sensitive to lectin-induced NK-cell-mediated cytotoxicity while others were completely resistant; resistance or susceptibility to cytotoxicity was not directly correlated with the ability of lectins to bind to the target cell. The lectin-induced cytotoxicity was independent of interferon (IFN) since detectable levels of IFN were not produced in the cultures of lectins and effector cells, cytotoxicity was not increased when exogenous IFN was added to the assay, and inhibitors of RNA and protein synthesis, which block the action of IFN, had no effect on the cytotoxicity. These results indicate that NK cells can mediate lectin-induced cytotoxicity and the implications of lectin interaction with NK cells are discussed. (Author abstract) (47 Refs)

129. PROTECTION OF NEWBORN MICE FROM A LETHAL HERPES SIMPLEX VIRUS INFECTION BY HUMAN INTERFERON, ANTIBODY, AND LEUKOCYTES.

Kohl S, Loo LS, Greenberg SB
Program Infectious Diseases, Univ. Texas Medical Sch., P.O. Box 20708, Houston, TX, 77025
J Immunol; 128(3):1107-1111 1982

Newborn mice infected ip with a lethal dose of herpes simplex virus (HSV) were protected by a combination of human interferon and human mononuclear cells (MC) when it was administered ip 1 day before infection (35.2% survived, p less than 0.001). The HSV immune status of the MC donors did not affect this protection. The number of MC required in the presence of 100 units of interferon was 5 x 10(6) to 5 x 10(5)/ mouse. The dose of interferon required in the presence of 5 x 10(6) MC was 100 to 10 U. Highest survival was achieved with 5 x 10(6) MC and 100 U of interferon. The active human effector cell in this system was either a lymphocyte or a monocyte-macrophage but not a polymorphonuclear leukocyte. Treatment of mice with interferon and MC after viral inoculation was not successful. Protection by human WISH cells (a non-leukocyte) and interferon was demonstrated (55% survival, p less than 0.001), which suggested that protection was due to interferon induced cross-species active antiviral protein production. The human interferon stimulated human but not murine or WISH cell natural killer cytotoxicity (NKC) in vitro. Mice receiving human interferon, MC, and subneutralizing doses of anti-HSV antibody before HSV infection were almost completely (95.2%) protected, and were protected significantly better (p less than 0.001) than mice receiving either MC plus interferon or MC plus antibody. Although adult MC could mediate this protection, all mice receiving MC from neonatal humans plus antibody and interferon died (p less than 0.001). In vitro experiments showed that protection was not due to viral neutralization. This is the first evidence for either in vivo human antiviral NKC or cross-species antiviral protein protection as well as defective in vivo human neonatal MC function in this system. (Author abstract) (29 Refs)

130. EFFECT OF INTERFERON ON THE INHIBITION OF THE GROWTH OF MALIGNANT CELLS BY HUMAN PERIPHERAL LEUKOCYTES. III. INFLUENCE OF SYSTEMIC ADMINISTRATION.

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C R Soc Biol (Paris); 175(6):904-909 1981

Effects of human WBC interferon (IFN) on spontaneous tumor cell growth inhibition (STCI) by human peripheral lymphocytes and on natural killer (NK) activity was studied in cultures of 10(5) HeLa cells and in 19 patients with malignant tumors (3 cervical, 6 lung, 4 tongue, 1 breast, 1 stomach, and 4 brain tumors) and in 11 patients with chronic type B hepatitis. Less STCI was noted in patients with cancer or hepatitis than in normal subjects. In vitro responses to IFN were the same for healthy subjects and patients. No significant increase in STCI was observed during the 24 hr after IFN administration, while NK activity was augmented. When IFN (10(6) IU during wk 1, 0.5 x 10(6) wk 2, 0.2 x 10(6) wk 3, and 10(5) wk 4) was administered systemically to the cancer and hepatitis patients, STCI gradually increased while NK activity was increased only after 10(6) IU and 0.5 x 10(6) IU of IFN were administered. The results indicated that systemic administration of IFN to patients with cancer or chronic hepatitis augmented the inhibition of STCI by human peripheral lymphocytes as well as NK activity. A difference between NK cells and effector cells for STCI was demonstrated. (4 Refs) (In FRE)

131. A SINGLE MONOCLONAL ANTI-IA ANTIBODY INHIBITS ANTIGEN-SPECIFIC T CELL PROLIFERATION CONTROLLED BY DISTINCT IR GENES MAPPING IN DIFFERENT H-2 I SUBREGIONS.

Germain RN, Bhattacharya A, Dorf ME, Springer TA
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Immunol; 128(3):1409-1413 1982

A xenogeneic rat anti-mouse Ia monoclonal antibody, M5/114 (gamma2b,kappa) was studied for its effects in vitro on T cell proliferative responses. Strain distribution studies revealed that M5/114 could inhibit I-A subregion-restricted T cell responses of the H-2b,d,q,u but not the H-2f,k,s haplotypes, indicating that this xenoantibody recognizes a polymorphic determinant on mouse Ia molecules. This same monoclonal antibody was found to inhibit BALB/c(H-2d) T cell proliferation to both G60A30T10 and G58L38phi4. The Ir genes regulating responses to these antigens map to either the I-A subregion (GAT), or the I-A and I-E subregions (GLphi), raising the possibility that M5/114 recognizes both I-A and I-E subregion-encoded Ia glycoproteins. It could be shown, using appropriate F1 responding cells, that M5/114 does in fact affect GAT and GLphi responses by interaction with both the I-A and the I-E subregion products, and not by an nonspecific effect resulting from binding to the I-A subregion product alone. These results are consistent with genetic and biochemical studies directly demonstrating that M5/114 recognizes AalphaAbeta and EalphaEbeta molecular complexes. The existence of a shared epitope on I-A and I-E subregion products suggests the possibility that these molecules arose by gene duplication. Finally, the precise correlation between the Ia molecules reco gnized by M5/114 and the ability of this antibody to block T cell responses under Ir gene control strengthens the hypothesis that Ia antigens are Ir gene products. (Author abstract) (33 Refs)

132. ANTIGEN-SPECIFIC SUPPRESSION OF CYTOTOXIC T CELL RESPONSES: AN IDIOTYPE-BEARING FACTOR REGULATES THE CYTOTOXIC T CELL RESPONSE TO AZOBENZENEARSONATE-COUPLED CELLS.

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J Immunol; 128(3):1188-1191 1982

When A/J mice are injected sc with azobenzenearsonate-(ABA) coupled spleen cells, their splenocytes contain primed ABA-specific cytotoxic T lymphocyte (CTL) precursors. Animals that are not primed in vivo do not develop vigorous CTL activity when assessed after in vitro culture with ABA-coupled stimulators. Suppressor molecules derived from ligand-induced first-order ABA-specific suppressor T cells were evaluated for their ability to limit cytolytic T cell development. We have shown that an idiotype-bearing, hapten-specific suppressor factor suppresses priming for CTL in an H-2-unrestricted but allotype-restricted manner. The implication of these studies to regulatory networks is discussed. (Author abstract) (15 Refs)

133. THE EFFECT OF IRRADIATION ON THE ANTIBODY ENHANCING HELPER T CELLS.

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Int J Radiat Biol; 41(1):1-13 1982

Helper T cells specific for sheep erythrocytes were generated in lethally irradiated mice. The helper effect exerted by these cells was determined in vitro in spleen cell cultures. Irradiation of the helper cells in vivo or in vitro with 1-9 Gy resulted in a bimodal relation between radiation dose and helper effect when measured either immediately or 6 hr after irradiation. The dose-effect curve became nearly linear when tested 20 hr after irradiation. These results indicated that the helper population consisted of about 80% of cells inactivated shortly after irradiation, possibly due to interphase death, and a second type showing a more retarded cell death. The latter cells were able to exert a helper function during the interval between irradiation and cell death. (Author abstract) (32 Refs)

134. IN VITRO AND IN VIVO CYTOTOXICITY OF 6 AMINO-5-FORMYL-METHYLAMINO-1,3-DIMETHYL URACIL, A URACILIC METABOLITE OF CAFFEINE.

Garattini S, Erba E, Morasca L, Peri G, Mantovani A, Filippeschi S, Spreafico F, Arnaud M

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Toxicol Lett; 10(2):313-319 1982

In vitro and in vivo cytotoxicity of 6 amino-5-formyl-methylamino-1,3-dimethyluracil (ADMU), a metabolite of caffeine, was investigated in rats and compared with cytotoxicity of 5-fluoroura cil (5FU). Cytotoxicity was evaluated by cell counts or (3H)thymidine incorporation in murine Lewis lung carcinoma (3LL) and L929 fibroblast cells and in the human E cell line derived from an ovarian carcinoma. ADMU did not affect proliferative capacity of the murine 3LL or L929 cells up to concentrations of 60 ug/ml or of the human E cell line. Dose-dependent inhibition of tumor cell proliferation and (3H)thymidine incorporation was observed after in vitro exposure to 5FU. A significant reduction of lymphocyte blastogenesis was observed following treatment with 1 ug/ml 5FU. Ten ug/ml 5FU completely abolished the lymphoproliferative response. ADMU concentrations ranging from 0.1 to 100 ug/ml showed no such response. ADMU (40 mg/kg, bid for 3 days) had no consistent effect on L1210 leukemia cells; a slight decrease in tumor cell number was observed on day 6. However, 5FU (25 mg/kg, bid for 3 days) was highly active in vivo against L1210 leukemia cells. No apparent in vitro cytotoxic effects were demonstrated with ADMU, but possible teratogenic effects have not been ruled out. (10 Refs)

135. GLUTATHIONE DEPLETION SENSITIZES TUMOR CELLS TO OXIDATIVE CYTOLYSIS.

Arrick BA, Nathan CF, Griffith OW, Cohn ZA
Lab. Cellular Pysiology and Immunology, Rockefeller Univ., New York, NY, 10021
J Biol Chem; 257(3):1231-1237 1982

Activated macrophages and granulocytes lyse tumor cells in the presence of phorbol myristate acetate or antitumor antibody via the secretion of reactive oxygen intermediates, such as H2O2. We compared the lysis of GSH-depleted or normal tumor cells by oxidants generated with glucose oxidase or activated macrophages and granulocytes. Two independent methods were employed to deplete cells specifically of GSH: (1) inhibition of GSH biosynthesis with buthionine sulfoximine, a selective inhibitor of gamma-glutamylcysteine synthetase, and (2) treatment with 1-chloro-2,4-dinitrobenzene (CDNB), which covalently binds GSH as catalyzed by endogenous GSH S-transferase. Incubation of P388 lymphoma or P815 mastocytoma cells with 0.2 mM buthionine sulfoximine resulted in a 50% reduction in GSH content by 4.5-5 hr and greater than 90% depletion by 15 hr. Treatment of P815 cells with CDNB for 15 min resulted in a dose-dependent loss of GSH, with a maximal depletion of approx 70% obtained with 10 uM CDNB. GSH depletion of P815 and P388 markedly enhanced their sensitivity to lysis by a flux of H2O2. Such cells could be lysed by dilutions of glucose oxidase and numbers of phorbol myristate acetate-stimulated granulocytes and activated macrophages which were ineffectual against untreated tumors. Recovery of tumor cell resistance to H2O2 after GSH depletion by either buthionine sulfoximine or CDNB followed the same time course as resynthesis of cellular GSH. These results and the previous finding that inhibition of the GSH redox cycle of tumor cells enhances both macrophage- and glucose oxidase-mediated cytolysis demonstrate the importance of GSH to tumor cell antioxidant defenses. (Author abstract) (43 Refs)

136. RECENT STUDIES ON ANTIBIOTICS AND SMALL MOLECULAR IMMUNOMODULATORS WITH POTENTIAL USEFULNESS IN TREATING LUNG CANCER: PART II-SMALL MOLECULAR WEIGHT IMMUNOMODULATORS PRODUCED BY MICROORGANISMS.

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Int J Clin Pharmacol Ther Toxicol; 20(1):19-23 1982

A screening method based on inhibition of cell surface enzymes was used to identify small mol wt compounds that bind to cells. Bestatin, amastatin, forphenicene, and esterastin were identified by this means. Detailed studies of bestatin on mouse and human immune systems are reported. A clinical study indicated that bestatin may enhance the effect of chemotherapy by restoring the reduced cellular immunity. The chemotherapy may aid the bestatin effect by destroying the mass of cancer cells and possibly destroying preferentially the suppressor cells. (18 Refs)

137. AUTOREGULATION OF THE IMMUNE RESPONSE.

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The Handbook of Cancer Immunology: Volume 9- Humoral Immunity in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 289 pp., 1981.

Animal experiments show that immune responses to a variety of antigens are modified by the subsequent production of autoanti-idiotypic antibodies (AID-Ab), which suppress the original response in a manner consistent with the presence of a functioning idiotype (ID) network. The formation of AID-Ab may play an important role in IgE-mediated immediate hypersensitivity reactions, general maternal-fetal interrelationships, and tumor immunity. The transplacental passage of maternal AID-Ab (via IgG) to the fetus can permanently suppress the formation of ID clones by the fetus. The fetus can mount effective immune responses specific for epitopes on maternal IgG. The formation of AID-Ab in tumor-bearing hosts may have a variety of effects, including either enhancement or inhibition of the activities of cytolytic effector T-lymphocytes. (52 Refs)

138. IMMUNOREGULATION VIA MODIFIED AMINO GROUPS.

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Transplantation Immunology Lab., Montefiore Hosp., Medical Center, Albert Einstein Coll. Medicine, Bronx, NY, 10467
The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

The T-lymphocytes are thought to be the primary mechanism of host defense against tumor growth, although many other cells are involved. Sodium cyanate (NaCNO) blocks antigen recognition by (or the activation of) suppressor T-cells, without apparently affecting the memory cells or the 'homing in' of migrating lymphocytes. NaCNO is specific for the T-cell receptor and does not affect the efferent arc of the immune response. NaCNO is directly toxic to a variety of tumors, selectively inhibiting DNA and protein synthesis. The simultaneous administration of deoxycorticosteroid can cancel the immunosuppressive effects of NaCNO on T-cell helper and cytotoxic killer cells. One major goal of tumor immunotherapy is boosting and steering the aberrant immune response to a pathway leading to the destruction of transformed cells. The success of this treatment depends on the initiation of a tumoricidal immune attack which can kill the tumor before suppressive factors or tumor size can inhibit the immune response. NaCNO may be suitable for such immunotherapeutic protocols. (163 Refs)

139. MODIFICATION OF AGE-RELATED IMMUNE DECLINE IN MICE DIETARILY RESTRICTED FROM OR AFTER MIDADULTHOOD.

Weindruch R, Gottesman SR, Walford RL
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Proc Natl Acad Sci USA; 79(3):898-902 1982

Although weaning-initiated dietary restriction of rodents is known to increase max survivorship and inhibit spontaneous late-life disease and immunologic aging, restriction begun in adulthood has been much less thoroughly evaluated. In the present studies, male mice of a long-lived F1 hybrid strain were gradually restricted dietarily beginning at 12 mo or older until their body wt stabilized at 60-70% of controls. Underfeeding decreased the number of nucleated cells per spleen but increased the percentage of T cells. For mice restricted at 12, 17, or 22 mo and tested at various ages thereafter, the [3H]thymidine uptake of spleen cells after phytohemagglutinin stimulation significantly exceeded values for age-matched unrestricted controls. Restriction did not, however, alter either splenocyte responses to concanavalin A or to B-cell mitogens or phytohemagglutinin stimulation significantly exceeded values for age-matched unrestricted controls. Restriction did not, however, alter either splenocyte responses to concanavalin A or to B-cell mitogens or phytohemagglutinin responses of peripheral lymph node cells. In the splenic plaque-forming cell response to injected sheep erythrocytes, restricted and control mice differed more clearly in response kinetics than in peak levels. The splenic cell-mediated lymphocytotoxic response to alloantigens was comparable in old mice (27-29 mo) restricted since 12 mo of age with that of young (5-to 6-mo) controls and was greater than that of age-matched old controls. Spontaneous tumors were observed less frequently in 19-to 25-mo-old mice restricted at 12 mo of age than in mice restricted at 17 mo or in controls. Our results indicate that appropriate food restriction initiated in adulthood influences immunosenescence and spontaneous tumor incidence in a fashion not unlike its weaning-initiated counterpart. (Author abstract) (31 Refs)

140. NEW DEVELOPMENTS IN RENAL TRANSPLANTATION IMMUNOLOGY.

Kerman RH
Div. Immunology and Organ Transplantation, Dept. Surgery, Univ. Texas Medical Sch., Houston, TX
Cancer Bull; 33(6):281-286 1981

Renal transplantation immunology is reviewed, with a focus on factors influencing graft survival. Topics include HLA tissue typing, donor-specific crossmatching, pretransplant nonspecific immune evaluation, influence of random blood transfusions on cadaveric renal allograft survival, and immunosuppression. Conventional immunosuppressive agents are discussed together with agents that may selectively suppress graft rejection while preserving immune function; the latter agents include antithymocyte globulin, monoclonal anti-T-cell subset antibody, and cyclosporin A. (29 Refs)

141. IMMUNOMODULATION WITH THYMIC HORMONES IN NEOPLASTIC DISORDERS.

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Dept. Developmental Therapeutics, Univ. Texas M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(6):265-271 1981

The interaction between thymic hormones and T-cell subsets in neoplastic disorders is discussed. Topics include the endocrine role of the thymus gland, thymosin fraction V, biologic studies with thymosin, thymic humoral factor, facteur thymique serique, thymopoietin II, and the role of thymic hormones in treatment of cancer. Studies with crude thymic extracts should be replaced by studies with well-characterized thymic peptides in well-defined groups of cancer patients. (67 Refs)

142. AUGMENTING AGENTS IN CANCER THERAPY.

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Dept. Clinical Immunology and Biological Therapy, Univ. Texas M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(6):261-265 1981

Augmenting agents, defined as natural or synthetic materials with the capacity to increase host defense mechanisms nonspecifically by activating host defense cells, are discussed with regard to cancer therapy. After in vivo administration, augmenting agents induce production by increased amounts of lymphokines and cytokines, such as interferon, which activate monocytes, macrophages, and the reticuloendothelial system and which activate natural killer cells and antibody-dependent cell-mediated cytotoxicity. Augmenting agents include intact microbes (BCG, inactivated streptococci OK 432), crude microbial fractions (Staph phage lysates, methanol extraction residue of BCG, cell wall fractions of various organisms), highly purified microbial fractions (peptidoglycans, glycolipids, glucans, lipopolysaccharide), and synthetic agents (pyran copolymer, pyrimidinols, lysolecithin analogs). (31 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

143. POSSIBLE ROLE OF MACROPHAGE-LIKE SUPPRESSOR CELLS IN THE ANTI-TUMOUR ACTIVITY OF BCG.

Castes M, Lynch NR, Lespinats G, Orbach-Arbouys S
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Br J Cancer; 44(6):828-837 1981

The iv injection of high doses (3 mg) of BCG into C3H mice bearing a transplantable 3-methylcholanthrene-induced fibrosarcoma caused the regression of a significant proportion. This effect was most evident when the BCG was injected on the day of the graft, or 7 days later. The injection of this agent either 14 days before the graft, or in low doses (0.1 or 0.5 mg), or directly into the tumor (it) only prolonged the survival of the animals. Spleen cells from systemic high-dose BCG-treated mice were found to exert a strong nonspecific cytostatic effect in vitro that was not an artefact of the test conditions, and was not expressed by cells from low-dose animals. The cytostatic effect was shown to be caused by cells with the characteristics of macrophages, ie they were strongly adherent, unaffected by treatment with anti-Thy 1.2C', radioresistant but heat-sensitive, and were detected in BCG-treated 'B' mice. The spleens of high-dose BCG-treated mice also contained suppressor cells that were capable of inhibiting the in vitro reactivity of normal T cells to PHA. Like the cytostatic effect, this suppressor activity was not detected in low-dose mice, and the cells responsible had the properties of macrophages; the effect was lost after the removal of adherent cells by sequential exposure to plastic and colloidal iron, but was conserved after treatment with anti-Thy 1.2C'. T-cell-deprived animals, such as 'B' or nude mice, also developed suppressor-cell activity when treated with systemic high-dose BCG. Close parallels became evident between the in vivo anti-tumor activity of BCG, the in vitro cytostatic effect, and the suppressor-cell activity. We here discuss the possible role of suppressor cells in the mechanism of action of this agent. (Author abstract) (38 Refs)

144. INHIBITION OF BETA-ADRENERGIC STIMULATION OF LYMPHOCYTE ADENYLATE CYCLASE BY PHORBOL MYRISTATE ACETATE IS MEDIATED BY ACTIVATED MACROPHAGES.

Novogrodsky A, Patya M, Rubin AL, Stenzel KH
Rogoff-Wellcome Medical Res. Inst., Beilinson Medical Center, Petah-Tikva, Israel
Biochem Biophys Res Commun; 104(2):389-393 1981

The in vitro effect of phorbol-12-myristate-3-acetate (PMA) on isoproterenol-stimulated adenylate cyclase in human peripheral blood mononuclear cells (PBM) was investigated with radioimmunoassay for cyclic AMP. PMA inhibited the isoproterenol-stimulated adenylate cyclase system in PBM but not in purified T-cells or in membrane preparations from turkey erythrocytes. Oxygen-derived radicals produced by PMA-activated macrophages evidently caused the inhibition. (12 Refs)

145. DIFFERENTIAL SENSITIVITY OF TWO MURINE LEUKAEMIA SUBLINES TO CYTOLYSIS BY CORYNEBACTERIUM PARVUM-ACTIVATED MACROPHAGES.

Berd D, Mastrangelo MJ
Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111
Br J Cancer; 44(6):819-827 1981

We observed the growth of two sublines of leukemia L1210 in histocompatible DBA2 mice given 10(3) cells ip and studied the protective effect of Corynebacterium parvum (CP). The growth of subline L1210-M was unaffected by pretreatment with CP or admixture with 10(5) peritoneal cells (PC) from CP-treated mice. In contrast, the growth of subline L1210-C was inhibited; CP pretreatment increased the proportion of long-term survivors (70% vs 20%) and admixture with CP-PC prolonged the survival time (59 days vs 49 days; p less than 0.05). In vitro experiments indicated that Sublines M and C were equally sensitive to cytostasis by CP-PC, as measured in a terminal labeling assay (greater than 90% inhibition of proliferation). However, subline C was much more sensitive to cytolysis (18h 125IUDR-release assay) by CP-PC; percentage specific release from L1210-C was at least 90%, whilst from L1210-M it was generally less than 25%. The differential susceptibility of the two sublines to cytolytic PC was maintained through 75 passages in culture. The effector cells were considered to be macrophages, because they were adherent, phagocytic, and sensitive to silica. Cytolysis was unrelated to endotoxin contamination, because it was not inhibited by polymyxin B, and was inhibited by pre-incubating PC in culture medium for 24 or 48 hr before adding target cells. Thus the relevance of nonspecific macrophage-mediated cytotoxicity in vitro to tumor resistance in vivo may depend on the strength of the cytotoxic reaction. (Author abstract) (18 Refs)

146. INFLUENCE ON THE CELL CYCLE PROGRESSION OF HELA CELLS BY C PARVUM ACTIVATED MACROPHAGES.

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J Reticuloendothel Soc; 31(1):85-98 1982

Dual parameter flow cytometry has been utilized to study the effect of C parvum activated mouse macrophages on HeLa cells. Identification of tumor cells in the presence of macrophages was facilitated by their distinct fluorescence with propidium iodide and fluorescein conjugated antiplacental alkaline phosphatase (PAP). The two parameters determined simultaneously provided an accurate quantitative assessment of HeLa cells. Dose response relationships between normal (NMphi) and C parvum (CpMphi) activated macrophages simultaneously assayed by tritiated thymidine (3HTdR) incorporation or direct assessment of the absolute number of tumor cells per well indicated that flow cytometry was a sensitive method of determining growth inhibition and cytotoxicity. Following incubation with CpMphi, the majority of HeLa cells appeared to survive in the G0G1 phase of the cell cycle, irregardless of whether or not both growth inhibition and cytoxicity had occurred. HeLa cells isolated in the G0G1 phase by unit gravity sedimentation were readily destroyed by CpMphi. Surviving tumor cells did not enter into S phase. The large increase in PAP on these cells indicated their viability in this growth arrested state. Target cells predominantly in late S and G2 phase were also sensitive to the cytolytic mechanism of CpMphi. However, the surviving cells were apparently not growth inhibited until they had passed through mitosis and entered the G1-S interphase. Prelabeled HeLa cells separated into different proportions of the various cell cycle phases were equally sensitive to activated macrophages. The results indicate that while cytotoxicity appears to occur throughout the cell cycle, growth inhibition is more specific and is a result of a block at or near the G1-S interphase. (Author abstract) (18 Refs)

147. ENHANCEMENT OF RAT AND HUMAN PHAGOCYTE SUPEROXIDE ANION RADICAL PRODUCTION BY CADMIUM IN VITRO.

Amoruso MA, Witz G, Goldstein BD
Dept. Environmental and Community Medicine, Rutgers Medical Sch., Piscataway, NJ, 08854
Toxicol Lett; 10(2/3):133-138 1982

The mechanism by which cadmium produces the superoxide anion radical (02-) was investigated in digitonin-stimulated phagocytes from man and rat. Cd concentrations ranging from 3.6 x 10(-2) to 3.6 x 10(-4) M inhibited 02-production in digitonin-stimulated human granulocytes or rat alveolar macrophages in a dose-dependent fashion. A concentration of 3.6 x 10(-5) M Cd markedly increased 02-production in the cells. Rat alveolar macrophages stimulated with phorbol myristate acetate showed a 100% reduction in 02-production in the presence of 3.6 x 10(-2) M cadmium chloride and a 20% reduction at 3.6 x 10(-5) M cadmium chloride. The results offer a possible explanation for the oxidizing effects of Cd in vivo. (14 Refs)

148. RESIDENT MACROPHAGE PROLIFERATION IN MICE DEPLETED OF BLOOD MONOCYTES BY STRONTIUM-89.

Sawyer RT, Strausbach PH, Volkman A
(c/o Volkman) Dept. Pathology and Lab. Medicine, East Carolina Univ. School Medicine, Greenville, NC, 27834
Lab Invest; 46(2):165-170 1982

The capacity of resident peritoneal macrophages and alveolar macrophages for self-renewal was studied in CD-1 mice depleted of radiosensitive blood monocyte precursors by irradiation of the bone marrow with the bone-seeking isotope 89Sr. Thermoluminescent dosimetry and studies of DNA synthesis showed that significant levels of radiation were absorbed predominantly in anatomical sites in close proximity to bone. Cell proliferation remote from bone marrow was unaffected when quantitated by DNA pre cursor uptake. Between 10 and 15 days after injecting mice intravenously with 89Sr at 2 uCi per gm of body weight, monocytes were only rarely detectable in the peripheral blood as determined by morphology, stains for nonspecific esterase and peroxidase, and by latex phagocytosis. Total numbers of resident peritoneal and alveolar macrophages were not significantly decreased and tritiated thymidine incorporation in vivo persisted at normal levels rather than regressing at a predicted rate during profound monocyte depletion. The data, therefore, suggest that local proliferation by resident macrophages in monocytopenic and intact mice is an important mechanism of population renewal. (Author abstract) (29 Refs)

149. IMMUNOCHEMICAL AND FUNCTIONAL ANALYSIS OF IA-LIKE ANTIGENS ON HUMAN MONOCYTE-MACROPHAGES WITH MONOCLONAL ANTIBODIES.

Ng AK, Zhang YH, Russo C, Ferrone S
Dept. Pathology, Columbia Univ., 630 W. 168th St., New York, NY, 10032
Cell Immunol; 66(1):78-87 1982

The distribution, structural profile, and functional properties of Ia-like antigens synthesized by human monocyte-macrophages have been analyzed using monoclonal antibodies to common determinants of these antigens. Up to 45 and 70%- of monocyte-macrophages isolated from the fluid of blisters induced with cantharidin and from peripheral blood, respectively, react with monoclonal antibodies to human Ia-like antigens. The level of Ia-like antigens on monocytes-macrophages appears to be similar to that on cultured B lymphoid cells. Monoclonal antibodies to common determinants of Ia-like antigens specifically block antigen presentation by monocyte-macrophages to T lymphocytes as well as proliferative response to T lymphocytes to autologous and allogeneic monocytes-macrophages. These results indicate that common determinants of Ia-like antigens play a role in the interaction of monocytes-macrophages with T lymphocytes. (Author abstract) (28 Refs)

150. INABILITY OF TUMOUR CELLS TO ELICIT THE RESPIRATORY BURST IN CYTOTOXIC, ACTIVATED MACROPHAGES.

Bryant SM, Hill HR
(c/o Hill) Dept. Pathology. Univ. Utah Coll. Medicine, Salt Lake City, UT, 84132
Immunology; 45(3):577-585 1982

Activated macrophages from Corynebacterium parvum-treated mice are cytotoxic to non-antibody-coated tumor cells and have an augmented respiratory burst potential when compared to resident macrophages. We have investigated the possible involvement of the respiratory burst as an effector mechanism in this type of tumor killing. Scavengers of toxic metabolites of oxygen such as catalase, superoxide dismutase, 2,3-dihydroxybenzoate, ethanol, and cytochrome c did not inhibit macrophage cytotoxicity in this system. To investigate whether or not neoplastic cells stimulate the macrophage respiratory burst, we exposed activated macrophages to viable tumor cells and monitored macrophage superoxide anion prod uction, chemiluminescence, and hexose monophosphate shunt activity. None of these indicators of the macrophage respiratory burst was stimulated by the tumor cells towards which the macrophages were cytotoxic. The data suggest that the respiratory burst is not utilized as an effector mechanism in the non-antibody-mediated macrophage tumor cytotoxicity reaction. (Author abstract) (25 Refs)

151. FACTORS PRODUCED BY MACROPHAGES AND TUMOR CELLS: INFLUENCE ON THE GRANULOCYTIC PRECURSOR CELLS (CFU-C) IN NORMAL AND TUMOR-BEARING MICE.

Pessina A, Brambilla P, Villa S, Marocchi A, Mocarelli P
Dept. Pathology, Hosp. Desio, Desio, Milan, Italy
J Cancer Res Clin Oncol; 102(3):235-244 1982

Some tumors are known to produce colony-stimulating factors (CSF). In mice bearing sc Ehrlich tumor (ET) we observed that tumor growth is responsible for hemopoietic perturbations in which the increase of granulocytic-macrophagic precursors (CFU-C) in bone marrow and in the spleen represents a remarkable aspect. CFU-C in bone marrow from ET-bearing mice are more sensitive than CFU-C from normal mice to CSF from L-cells (LC-CM), mouse embryo fibroblasts (MEF-CM) and from the same tumor (ET-CM). Macrophages from normal and from ET-bearing mice exert the same effect on the proliferation of normal bone marrow CFU-C. Bone marrow CFU-C from ET-bearing mice shows an increased sensitivity to the inhibitory factors produced by macrophages from ET-bearing mice. (Author abstract) (17 Refs)

152. ANTIGEN PRESENTATION TO T CELL HYBRIDOMAS BY A MACROPHAGE CELL LINE: AN INDUCIBLE FUNCTION.

Birmingham JR, Chesnut RW, Kappler JW, Marrack P, Kubo R, Grey HM

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J Immunol; 128(3):1491-1492 1982

We have investigated the ability of an Ia-, nonantigen-presenting macrophage tumor cell line, P338D1 (H-2d), to present antigen to T cell hybridomas after incubation in a lymphokine-containing preparation. P388D1 cells were incubated in microtiter wells with various concentrations of Con A-stimulated spleen cell supernatants. Antigen-specific stimulation of H-2d-restricted, KLH-specific T cell hybridomas was observed by P388D1 incubated with SUP.P338D1 cells incubated for 3 days in medium or control SUP did not present antigen. In addition, no sumulation of T hybridomas was seen by P388D1 in the presence of an unrelated antigen. The response could be inhibited by the appropriate monoclonal anti-Ia reagents. These results demonstrate that a macrophage tumor cell line can be induced to present antigen and provides for large numbers of readily available, homogeneous macrophages for studying the cellular and biochemical requirements for antigen processing and presentation. (Author abstract) (6 Refs)

153. THE ROLE OF MACROPHAGES AND OTHER CELLS IN CARCINOGENESIS.

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The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

Because the lung cancer incidence varies among smokers, there must be a range of individual susceptibilities to polycyclic aromatic hydrocarbons and other carcinogens. When the pulmonary alveolar macrophages (PAMs) are exposed to large amounts of carcinogens, the risk of tumorigenesis may depend on the relative ratios of the PAM fraction capable of enhancing protective responses (eg, phagocytosis and immunologic surveillance of transformed cells) and the PAM fraction capable of suppressing these protective mechanisms by such activities as aryl hydrocarbon hydroxylase (AHH) activation. Prospective studies in high-risk populations (eg, patients with asbestosis who continue to smoke) are needed to determine whether the degree of AHH activity can be used as a risk factor for lung cancer. Studies on the regulation of mechanisms for cytotoxic antibody production, cell-mediated tumor destruction, and nonspecific inflammatory responses may also help to assess the critical host responses involved in the eradication or retention of neoplastically transformed cells. (56 Refs)

154. MACROPHAGE ARGINASE, ARGININE CONSUMPTION, AND TUMORS.

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The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

Many human and mouse tumors contain large macrophage populations and high levels of arginase (ARGase), which may be synthesized by the macrophages. In several experimental tumors, the growth rate is inversely related to the ARGase activity. Selective tumor growth inhibition by arginine depletion or ARGase treatment has been demonstrated. ARGase is immunosuppressive in vitro, but its involvement in immunosuppression in vivo has not been demonstrated. These findings suggest that ARGase may be involved in tumor immunity, and that ARGase synthesis by macrophages may be an early defense against tumor growth. This hypothesis could be tested by feeding tumor-bearing animals with arginine-deficient diets, with or without treatment by canavanine and nonantigenic ARGase. (73 Refs)

155. MACROPHAGE REGULATION OF ANTITUMOR CYTOTOXICITY.

Vallera DA, Schmidtke JR
Dept. Surgery, Univ. Minnesota, Minneapolis, MN
The Handbook of Cancer Immunology: Volume 9- Humoral Immunity in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 289 pp., 1981.

Macrophages act as both accessory and stimulator cells in cell-mediated cytotoxi city. Macrophages are involved in syngeneic antitumor cytotoxicity and human neoplasms. The host's immune response to antigenic challenge (whether amplification, suppression, or tolerance) depends on macrophage-lymphocyte interactions, the antigen involved, and the many soluble factors of lymphocyte and macrophage origin taking part in the process. Macrophages are important accessory cells in the afferent phase of antitumor cytotoxicity; they are also involved in the host's efferent reactions against the tumor. (78 Refs)

156. MACROPHAGE ACTIVITIES IN SARCOMA 180-BEARING MICE AND EL4-BEARING MICE.

Kurashige S, Mitsuhashi S
Coll. Medical Care and Technology, Gunma Univ., Showa-machi 3-39-15, Maebashi 371, Japan
Gan; 73(1):85-90 1982

Four types of macrophage activities were studied in sarcoma 180-bearing ICR mice and EL4-bearing C57BL mice. Sarcoma 180 cells grow very slowly and do not metastasize, while EL4-cells grow very rapidly and metastasize rapidly to the liver. Chemotactic activity of macrophages was significantly reduced from an early stage in both sarcoma 180-bearing ICR mice and EL4-bearing C57BL mice as compared with that in normal mice. Digestive activity, which was determined by following O2-production by chemiluminescence measurements was also reduced from an early stage in tumor-bearing mice, whereas no reduction of engulfment activity of microorganisms was observed until an advanced stage in both sarcoma 180-bearing mice and EL4-bearing mice. In contrast enhancement activity of macrophages in the blastogenic response of spleen lymphocytes to bacterial lipopolysaccharide was retained at the normal level at the early stage of the tumor graft and was reduced in later stages. These results suggest that activities of Ia-negative macrophages were at first depressed generally in tumor-bearing hosts and later the activities of Ia-positive macrophages were depressed by factor(s) which might be produced by tumor cells. (Author abstract) (20 Refs)

157. DIFFERENTIATION OF MACROPHAGES FROM LEWIS LUNG CARCINOMA TUMOUR CELLS IN TISSUE SECTIONS BY THEIR ALPHA-NAPHTHYL BUTYRATE ESTERASE ACTIVITY.

Brown R, Wolman M
Dept. Pathology, Sackler Sch. Medicine, Tel-Aviv Univ., Tel-Aviv, Israel
Histochem J; 13(6):975-981 1981

A histochemical method is described that identifies macrophages around and inside of Lewis lung carcinoma (3LL). The activities of alpha-naphthyl butyrate esterase (ANBE), non-specific esterase (alpha-naphthyl acetate esterase), indoxyl esterase and acid phosphatase were studied histochemically in macrophages (from normal mice) grown in culture, 3LL cell cultures, and in tissue sections of primary tumors and metastases of 3LL. All macrophages in culture were stained by the procedure for ANBE while 3LL cells were unstained. In tissue sections macrophages were intensely stained by the ANBE procedure, while the tumor cells were not stained at all. In the sections, macrophages were readily distinguishable from 3LL cells. Non-specific esterase activity appeared as brown granules in both macrophages and 3LL cells. Indoxyl esterase and acid phosphatase were present in macrophages at the margin of the tumor only. The ANBE-positive macrophages differed in shape and location from those positive for acid phosphatase and indoxyl esterase. This may indicate a difference in characteristics between macrophages found inside a tumor and those found at the tumor margins. (14 Refs)

158. ALTERATIONS IN MICROFILAMENTOUS AND MICROTUBULAR STRUCTURES ACCOMPANIED BY CELL GROWTH OF SV40-TRANSFORMED CLONAL MACROPHAGES, LINE 28-12 AND ITS SUBLINE.

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Lab. Electron Microscopy, Dept. Bacteriology, Tottori Univ. Sch. Medicine, Yonago 683, Japan
Cell Struct Funct; 6(4):329-339 1981

Morphological patterns of sets of actively growing and stationary simian virus 40 (SV40)-transformed macrophages of the clonal line 28-12, obtained from SV40-infected cultures of mouse bone marrow cells, were compared with those of the slowly growing subline 28-12(Ara) isolated from cytosine arabinoside-treated cultures. Transmission and scanning electron microscopic observations revealed microfilamentous and microtubular structures in the cells. Bundles of 70 A microfilaments were found in fully-transformed, actively growing 28-12 cells but not in minimally-transformed, stationary 28-12 cells, an observation which inconsistent with other studies. A decrease in microtubules apparently occurs in actively growing cells which have high levels of SV40 T-antigen, although evidence is not unequivocal. Response of the cells to colchicine shows that cytoskeletal structures, including microtubules, are affected by transformation. The 28-12(Ara) cells, which are considered moderately transformed cells, have a significant amount of SV40 T antigen, fewer microtubules than either type of 28-12 cells, lower response to colchicine, and slower growth, but the cells also have a phagocytic capacity. (32 Refs)

159. THE INFLUENCE OF MONOCYTE (ADHERENT CELL) CONTENT IN HUMAN MONONUCLEAR BLOOD CELL POPULATIONS ON THE ESTIMATION OF INDIVIDUAL LEVELS OF N-ACETOXY-2-ACETYLAMINOFLUORENE INDUCED UNSCHEDULED DNA SYNTHESIS.

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Carcinogenesis; 3(1):39-43 1982

Human mononuclear blood cells were isolated from heparinized blood samples by centrifugation in Isopaque-Ficoll gradients. The isolated mononuclear cells were then subjected to further fractionation according to size by sedimentation at unit gravity. The faster sedimenting cells containing high proportions of monocytes were two-fold greater at carrying out N-acetoxy-2-acetylaminofluorene (NA-AAF) induced unscheduled DNA synthesis (UDS) than were cell fractions containing only lymphocytes. Furthermore, the mononuclear cell populations that adhere to plastic surfaces were shown to be responsible for the increased NA-AAF induced UDS observed for the cells that sediment at a faster rate in a unit gravity gradient. Interindividual fluctuations in NA-AAF induced UDS estimated on mononuclear blood cells could not be explained in terms of fluctuations in adherent cell (monocyte) NA-AAF induced UDS when the general population was examined. These data support the notion that although monocytes have a greater DNA repair synthesis, the variation in monocyte content and/or function encountered in the general population is not great enough to seriously affect interindividual comparisons of NA-AAF induced UDs. (Author abstract) (27 Refs)

160. LOWER RELAPSE RATES AFTER NEIGHBOURHOOD INJECTION OF CORYNEBACTERIUM PARVUM IN OPERABLE CERVIX CARCINOMA.

Mignot MH, Lens JW, Drexhage HA, Von Blomberg BM, Flier VD, Oort J, Stolk JG
Dept. Obstetrics and Gynecology, Free Univ. Hosp., Amsterdam, The Netherlands
Br J Cancer; 44(6):856-862 1981

The effect of adjuvant immunotherapy with a single neighborhood injection of 2 mg C parvum (CP) was investigated in a randomized study involving 43 patients with carcinoma of the cervix uteri, all of whom were treated by radical surgery. All patients had carcinoma confined to the cervix, the upper part of the vagina or the parametrial region. When the malignancy had spread to the parametrial region, additional postoperative radiotherapy was given. Twenty two patients received immunotherapy 10 days before surgery, whereas the remaining 21 control patients received no immune stimulation. Only minor side effects of CP were encountered. Follow-up shows a relapse rate of 5% in the CP treated group and of 29% in the controls (p less than 0.05). A further 15 patients with more advanced malignancies were added to our studies. In these, CP stimulation had no effect on relapse rates, but the relapse-free intervals were longer after immune stimulation: control 3.5 mo (mean) -1.5 (sd), CP 13.0 mo -7.0 (p less than 0.05). The number of peripheral T cells and the ability to become sensitized to DNCB were increased after CP stimulation. A decrease was found in the number of blood monocytes and the number of monocytes capable of transforming into active macrophages, indicating a possible sequestration of these cells in the tissues. (Author abstract) (40 Refs)

161. PERITONEAL ADHERENT CELLS INHIBIT THE GENERATION OF CYTOTOXIC T LYMPHOCYTES WITH PROSTAGLANDIN-MEDIATED SYSTEM.

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Dept. Immunology Cancer Res. Inst., Sch. Medicine, Kyushu Univ., 3-1-1, Maidashi, Higashi-ku, Fukuoka, 812, Japan
Cell Immunol; 66(1):195-201 1982

Responder spleen cells primed to alloantigens in vivo could generate high degree of cytotoxicity against low- or nonimmunogenic stimulators such as thymocytes or UV light-treated spleen cells in vitro. However, a removal of adherent cells from primed responder cells remarkably reduced the cytotoxicity after stimulation with such low-immunogeneic stimulators. Adding a small number of peritoneal adherent cells (PACs) also suppressed the cytotoxic activity of unseparated responders against low-immunogenic stimulators. These suppressive effects by PACs were blocked by indomethacin. By adding prostaglandin E2, cytotoxic T lymphocyte (CTL) generation of primed unseparated responders against low-immunogenic stimulators was suppressed; however, cytotoxic activity against mitomycin C-treated stimulators was not suppressed. These results suggested that prostaglandins released from PACs selectively inhibited the function of splenic adherent cells that were required for CTL generation of primed responder spleen cells against low-immunogenic stimulators in vitro. (Author abstract) (14 Refs)

162. ALLOREACTIVE CYTOTOXIC T LYMPHOCYTE RESPONSES TO H-2 PRODUCTS ON PURIFIED ACCESSORY CELLS.

Czitrom AA, Katz DR, Sunshine GH
Tumour Immunology Unit, Imperial Cancer Res. Fund, Dept. Zoology, Univ. Coll. London, Gower St., London WC1E 6BT, England
Immunology; 45(3):553-560 1982

Several purified accessory cell populations were examined for their capacity to stimulate allospecific cytotoxic T lymphocytes (CTL). A number of non-lymphoid accessory cells stimulated CTL directed against the whole H-2 region and to isolated Class I or Class II products of the major histocompatibility complex (MHC). The accessory cells which stimulated CTL expressed surface Ia. The generation of CTL to Class I MHC products could be inhibited by antisera directed at Class II molecules on the same accessory stimulator cell surface. These findings demonstrate the importance of Class II MHC products on heterogeneous accessory cells capable of stimulating alloreactive CTL. (Author abstract) (27 Refs)

ANTIBODY-DEPENDENT CELL-MEDIATED

CYTOTOXICITY

163. INHIBITION OF HUMAN ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY, CELL-MEDIATED CYTOTOXICITY, AND NATURAL KILLING BY A XENOGENEIC ANTISERUM PREPARED AGAINST 'ACTIVATED' ALLOIMMUNE HUMAN LYMPHOCYTES.

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Immunology Lab., St. Christopher's Hosp. for Children, 5th and Lehigh Ave., Philadelphia, PA, 19133
J Immunol; 128(3):1246-1251 1982

Xenogeneic antiserum (RH1) was prepared in Lewis rats by hyperimmunization with concanavalin A- (Con A) activated alloimmune human lymphocytes. The antiserum RH1 effectively inhibited human antibody-dependent cellular cytotoxicity (ADCC), cell-mediated cytotoxicity (CMC), and natural killing (NK) in the absence of complement (C). Inhibition by RH1 was dependent on the dilution of antiserum employed and the number of cytotoxic lymphocytes present during cytolysis. Pretreatment of lymphocytes with RH1 or the presence of RH1 in culture did not inhibit lymphocyte proliferation stimulated by Con A, phytohemagglutinin, or allogeneic cells; lymphokine production as measured by leukocyte-inhibiting factor production; antibody-dependent C lysis; or CMC mediated by murine cytotoxic T lymphocytes. Analysis of the mechanism of inhibition of cytotoxicity by RH1 revealed that (1) RH1 was not cytotoxic for human lymphocytes at 37 C in the absence of C; (2) purified F(ab')2 fragments were equally inhibitory as whole serum; (3) pretreatment of lymphocytes with RH1 effectively inhibited their capacity to mediate ADCC, CMC, or NK, and this effect was reversible by culturing the cells overnight at 37 C; (4) RH1 did not inhibit target cell binding by K cells, effector cells of ADCC, or alloimmune T cells, but did inhibit binding by NK cells, and finally, (5) the addition of RH1 to preformed lymphocyte-target conjugates in a single cell cytotoxicity assay inhibited killing of the bound target cells in all three systems without disrupting the conjugates. Collectively, these findings suggest that RH1 antiserum interacts with structures present on the surfaces of cytotoxic lymphocytes that are involved in the activation of the lytic mechanism(s) or with the actual lytic molecule or molecules themselves. Furthermore, the ability of RH1 to inhibit ADCC, CMC, and NK during the post-binding cytolytic phase of these reactions indicates that binding and cytolysis are distinct and separate events in all types of cell-mediated cytolysis. (Author abstract) (24 Refs)

164. NATURAL AND ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY TO CULTURED TARGET CELLS SUPERINFECTED WITH EPSTEIN-BARR VIRUS.

Takasugi M, Mickey MR, Levine PH
Dept. Surgery, UCLA Sch. Medicine, Univ. California, Los Angeles, CA, 90024
Cancer Res; 42(4):1208-1214 1982

The relationship between natural cell-mediated cytotoxicity (NCMC) and antibody-dependent cell-mediated cytotoxicity (ADCC) was examined in an Epstein-Barr virus-infected target cell system. The total ADCC reactivity to Epstein-Barr virus-infected target cells varied considerably with different effector cells, indicating contributions to specificity by the effector cells as well as by antibodies in the sera. To investigate the role of each reactant, the effector cells, sera, and target cells were tested according to a three-dimensional experimental design and examined for selectivity with the two- and three-way interaction analysis. The two-way analysis was applied to different planes from the experiment to examine special interactions involving two of the three reactants. Selective ADCC was examined through the results from sera versus target cells, selective NCMC was examined by effector cells versus target cells, and the relationship between NCMC and ADCC was examined through the final plane of effector cells versus sera. A three-way interaction analysis applied to the same results supported the conclusions from the two-way analysis and allowed further inquiry into the concurrent role of three reactants. The design and analysis used in the study allowed detection of selective ADCC and NCMC for Epstein-Barr virus-infected target cells and variations in the efficiency of ADCC by different effector cells and in the modulation of NCMC by different sera. (Author abstract) (21 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

165. NON-H-2 AND H-2-LINKED IMMUNE RESPONSE GENES CONTROL THE CYTOTOXIC T-CELL RESPONSE TO H-Y.

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Immunogenetics; 15(3):261-270 1982

The immunoregulation of cytotoxic T-cell responses to the male-specific antigen H-Y in mice has been found to be genetically controlled by genes of the major histocompatibility complex (H-2). Responsiveness was mainly confined to H-2b strains, but it has also been found in recombinant strains, F1 hybrids, and chimeras that carry at least part of the H-2b haplotype. By using a different immunization procedure it has been shown recently that an H-2k mouse strain (CBA) is also able to mount an equivalent H-Y-specific response. We investigate here, by appling this immunization technique, the responsiveness of other H-2k strains and of strains of other independent H-2 haplotypes. Both responders and nonresponders are found in three haplotypes: k, s, and d. The strain distribution pattern of responsiveness shows a combined influence of non-H-2 and H-2 genes. In certain strains there is a high variability in responsiveness between genetically identical individual animals. We discuss a model of immune response (Ir) gene function which could account for these observations. (Author abstract) (36 Refs)

166. T CELL-DERIVED B CELL DIFFERENTIATION FACTOR(S): EFFECT ON THE ISOTOPE SWITCH OF MURINE B CELLS.

Isakson PC, Pure E, Vitetta ES, Krammer PH
Dept. Microbiology, Univ. Texas Health Science Center at Dallas, Dallas, TX
J Exp Med; 155(3):734-748 1982

B cells from female BALB/c mouse spleen suspended in low-density culture were stimulated by lipopolysaccharide and tested for changes in Ig isotype secretion induced by several T-cell-derived supernatants. A T cell hybridoma (FS7-6.18) and the T cell lines PK 7.1.1a and PK 7.1.2, which can induce B cell differentiation, produced lymphokine(s) that enhanced IgG secretion by surface immunoglobulin cells and in particular the secretion of IgG1. The B cell differentiation factor(s) evidently differs from known lymphokines, such as T-cell-replacing factor, some colony-stimulating factors, macrophage-activation factors, and immune interferon. (61 Refs)

167. REGULATION OF IN VITRO CYTOTOXIC T LYMPHOCYTE GENERATION. I. EVIDENCE THAT KILLER CELL PRECURSORS DIFFERENTIATE TO EFFECTOR CELLS IN TWO STEPS.

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Dept. Surgery, Tufts Univ. Sch. Veterinary Medicine, Boston, MA, 02111
J Exp Med; 155(3):783-796 1982

The generation of cytotoxic T lymphocytes (CTL) in the murine system is apparently a two-step process. Step 1, induction of naive CTL (CTL-PN) to activated CTL (CTL-PA), is sensitive to the effects of in vitro generated suppressor T cells but is not inhibited by the addition of pyrilamine to the culture or heat inactivation of stimulator cells. Step 2, the differentiation of CTL-PA to CTL, can be blocked by pyrilamine but not by the same suppressor cells that inhibit the transition from CTL-PN to CTL-PA. The CTL-PA to CTL step and possibly the CTL-PN to CTL-PA step require T helper lymphocyte activity. (22 Refs)

168. IDENTIFICATION OF A T CELL-DERIVED B CELL GROWTH FACTOR DISTINCT FROM INTERLEUKIN 2.

Howard M, Farrar J, Hilfiker M, Johnson B, Takatsu K, Hamaoka T, Paul WE
Lab. Immunology, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
J Exp Med; 155(3):914-923 1982

Long-term culture of BALB/c mouse B lymphocytes in which induced supernatants from a T cell hybridoma (B151K12) sustain slow proliferation of lipopolysaccharide-activated B cells suggested the existence of a T cell-derived growth factor. Such a factor was identified in induced supernatants from mouse thymoma EL4 by gel filtration analysis. The B cell growth factor is distinct from interleukin 2. It co-stimulates with anti-IgM antibodies in short term cultures of purified B lymphocytes to produce polyclonal B cell proliferation but not antibody-forming cell production. The factor is not mitogenic for resting B cells and interacts with anti-IgM-activated B cells in a non-H-2-restricted manner. (28 Refs)

169. AN ALTERNATIVE APPROACH TO THE QUANTITATION OF GLUCOCORTICOID-RECEPTOR COMPLEXES IN THE NUCLEI OF LYMPHOID CELLS.

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Endocrinology; 110(3):708-716 1982

We have developed a rapid and convenient method for the quantitative assessment of nuclear translocation of glucocorticoid-receptor complexes in lymphoid cells. In this assay, cells are incubated with [3H]dexamethasone at 4 C or 21 C, treated for 15 min at 4 C with the sulfhydryl blocking reagent sodium tetrathionate or methyl methanethiolsulfonate, and then ruptured with the neutral detergent Triton X-100 to separate the nuclei from the cytoplasmic constituents. When cells are incubated with [3H]dexamethasone at 21 C, an av of 45-60% of the specifically bound cellular radiolabel remains with the nuclei. In contrast, less than 15% of the hormone remains with the nuclei when cells are labeled at 4 C. In rat thymocytes, quantitatively similar results were obtained using this new method and a conventional method of isolating nuclei (homogenization of cells in a hypotonic buffer). For both methods, preincubation of the labeled cells with the sulfhydryl blocking reagents was essential to prevent release of the nuclear hormone (or hormone-receptor complex) by a sulfhydryl-dependent labilizing activity apparently located in the cytoplasm. The new method has been successfully used to quantitate uptake of nuclear [3H]dexamethasone-receptor complexes in rat thymocytes, human lymphocytes, and human leukemia cells of lymphoid and myeloid origin. It should prove successful for separating nuclear from cytoplasmic glucocorticoid-receptor complexes in a wide variety of cells, many of which resist disruption by more conventional techniques. (Author abstract) (49 Refs)

170. LYSOSOMAL ENZYMES IN NORMAL AND LEUKEMIC B LYMPHOCYTES.

Kraaijenhagen RJ, Schipper-Kester GP, Rijksen G, De Gast GC, Staal GE
Unit Medical Enzymology, Dept. Hematology, State Univ. Hosp., Catharijnesingel 101, 3500 CG Utrecht, The Netherlands
Clin Chim Acta; 118(2/3):255-263 1982

Activities of 11 lysosomal enzymes (arylsulfatase A, beta-D-galactosidase, alpha-D-galactosidase, N-acetyl-beta-D-glucosaminidase A, N-acetyl-beta-D-glucosaminidase B, N-acetyl-alpha-D-glucosaminidase, beta-D-glucuronidase (BDG), arylsulfatase B (ASB), alpha-L-fucosidase, alpha-D-mannosidase, alpha-D-glucosidase (ADG), and acid phosphatase (AP)), were compared in total lymphocytes, T and non-T lymphocytes and monocytes from patients with chronic lymphocytic leukemia (CLL) and normal subjects, and the T lymphoblastic cell lines CCRF-CEM and CCRF-HSB-2 and the B lymphoblastic cell lines CCRF-SB and Raji. Except for AP, all enzyme activities were markedly lower in leukemic lymphocytes, which are all B lymphocytes. Activities of BDG and to a lesser extent AP were higher in T lymphocytes, whereas ASB and ADG were somewhat lower, but otherwise there was little difference between T and non-T lymphocytes. Comparison of lysosomal enzyme activities from leukemic B lymphocytes and normal, unseparated lymphocytes seems acceptable for most of the enzymes. With the cell lines, T and B lymphoblasts could not be distinguished enzymatically. Determination of lysosomal enzyme activities may be helpful in diagnosis of CLL. (14 Refs)

171. REACTIVITY OF MONOCLONAL ANTIBODIES AGAINST HUMAN LEUCOCYTE ANTIGENS WITH LYMPHOCYTES OF NON-HUMAN PRIMATE ORIGIN.

Neubauer RH, Levy R, Strnad BC, Rabin H
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J Immunogenet; 8(6):433-442 1981

A series of B- and T-lymphoid cells of human and nonhuman primates (gorilla, chimpanzee, orangutan, gibbon, baboon, owl monkey, marmoset) and fresh peripheral blood lymphocytes were used to examine phylogenetic distributions of the antigens present on human lymphocytes. These antigens were identified with murine monoclonal antibodies specific for a T-cell antigen, lymphoid and lymphoid:myeloid antigens, Ia antigens, and beta 2 microglobulin. Reactivity of the monoclonal antibodies was detected using anti-murine IgG reagent. Monoclonal antibodies directed against human leukocyte antigens react with other primate species in a pattern consistent with known phylogenetic relationships. Human antigenic determinants were restricted to the great apes (gorilla, chimpanzee) whereas the Ia antigens reacted with cells of both Old and

New World primate species. Immunoprecipitation analyses using 125I-labeled B-cell lines analyzed following sodium dodecyl sulfate polyacrylamide gel electrophoresis demonstrated that the molecular structures of the Ia antigens differ not only between human cells and cells of lower primates, but between those on owl monkey and marmoset cells. (35 Refs)

172. CYTOTOXIC EFFECTS OF BUTYRATE AND OTHER 'DIFFERENTIATION INDUCERS' ON IMMATURE LYMPHOID CELLS.

Bell PA, Jones CN
Tenovus Inst. for Cancer Res., Welsh Natl. Sch. Medicine, Heath Park, Cardiff CF4 4XX, Wales
Biochem Biophys Res Commun; 104(4):1202-1208 1982

The effects of sodium n-butyrate, salts of other short-chain fatty acids, 5-azacytidine, hypoxanthine, L-ethionine and dimethylsulfoxide were studied in CCRF-CEM human leukemic lymphoblasts, cells which have properties typical of immature lymphoid cells. These compounds were all cytotoxic to CEM cells at concentrations similar to those reported to produce reversible growth inhibition in more mature lymphocytes or growth inhibition and differentiation in other cell types. The incorporation of [6-3H]thymidine into acid-insoluble material by CEM-C7 cells was progressively inhibited by n-butyrate in a dose-dependent manner, with half-maximal inhibition at 0.4 milliM (mM). Cell lysis, as indicated by release of 14C-labeled chromatin fragments, was elevated above control level after cells were treated with 0.5 and 5 mM n-butyrate. The salts of related short-chain fatty acids showed the same rank of potency for cytotoxicity as that reported for the effects of these compounds on cell growth and differentiation in several other systems, including Friend erythroleukemia cells. Other studies showed that n-butyrate is progressively less toxic to CEM-C7 cells as growth rate is reduced by serum restriction. The inhibitory effects of these compounds on DNA methylation are postulated to be responsible for their cytotoxic actions. (24 Refs)

173. EXPRESSION OF ENDOGENOUS RETROVIRAL GLYCOPROTEIN 70 BY ANTIGEN-ACTIVATED CYTOTOXIC AND SUPPRESSOR T LYMPHOCYTES OF MICE.

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(c/o Wecker) Institut fur Virologie und Immunobiologie, Universitat Wurzburg, Versbacher Str. 7, 8700 Wurzburg, W. Germany
Proc Natl Acad Sci USA; 79(4,part1):1250-1253 1982

Concanavalin A-stimulated murine spleen cells and antigen-stimulated B lymphocytes of normal mice express an antigen that reacts with goat antiserum against glycoprotein (gp) 70. Structural analysis of this antigen characterizes it as endogenous virus gp70 that is most likely of xenotropic origin. Activated nonspecific T suppressor cells and cytotoxic T lymphocytes express endogenous viral gp70, whereas nonactivated mouse T or B lymphocytes do not. The presence of endogenous retroviral gp70 is thus a novel marker for activated mouse lymphocytes in general. (Author abstract) (37 Refs)

174. A NEW MURINE LYMPHOCYTE ALLOANTIGEN, LY-21.2, MAPPING TO THE SEVENTH CHROMOSOME.

Kennard J, Meruelo D
Irvington House Inst., Dept. Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016
Immunogenetics; 15(3):239-250 1982

Using a monoclonal antibody raised by fusing spleen cells from A/J mice, immunized with B10.A splenocytes and lymph-node cells, with a BALB/c myeloma, we have described a new surface alloantigen, Ly-21.2. Ly-21.2 is present in varying amounts in all lymphoid tissues, is not detectable in the brain, kidney, lung or erythrocytes, and is found in only trace amounts in the liver. Strain distribution studies showed that Ly-21.2 is present in all strains examined, including B10, except the A strain and segregation analysis of (A/J x B10)F2 mice showed that Ly-21.2 expression (1) is encoded by one gene and (2) is linked to albinism on chromosome 7. Studies performed on mice developing T-cell leukemia showed that, regardless of the etiologic agent, Ly-21.2 expression increases dramatically in mice with overt leukemia. In addition, preliminary studies suggest that expression of Ly-21.2 is linked to increased susceptibility of mice to Friend-virus-induced erythroleukemia. (Author abstract) (27 Refs)

175. NATURE AND BIOLOGICAL ROLE OF LYMPHOCYTOSIS IN THE HEMATOPOIETIC TISSUE OF LOCALLY IRRADIATED BONE MARROW.

Dygai AM, Gol'dberg ED, Melik-Gaikazian EV
Medical Inst., Tomsk, USSR
Radiobiologiia; 21(6):873-878 1981

The role of thymocytes in the regulation of the medullary hematopoiesis was studied in 950 BALB mice subjected to a whole-body or local irradiation at 65 rads/min (total dose 700 rads). One mo prior to irradiation, 100/950 mice were subjected to thymectomy. Local irradiation resulted in marked increase of the absolute lymphocyte count in the bone marrow of both irradiated and shielded ext remities. On day 6 after irradiation, the lymphocyte count in the bone marrow was 39x greater than that after whole-body irradiation. Lymphocytosis was not observed in thymectomized mice. Lymphocyte migration had stimulating effect on postradiation recovery of the hematopoiesis. Normalization of the total number of myelokaryocytes was observed on day 7, while the recovery of the bone marrow cellularity in thymectomized mice was observed only on day 14. (14 Refs) (In RUS)

176. DIFFERENTIATION OF C3B RECEPTORS ON HUMAN LYMPHOCYTES, PHAGOCYTES, ERYTHROCYTES AND RENAL GLOMERULUS CELLS BY MONOCLONAL ANTIBODIES.

Dierich MP, Mussel HH, Scheiner O, Ehlen T, Burger R, Peters H, Schmitt M, Trepke S, Zimmer G
Inst. Medical Microbiology, Johannes Gutenberg-Univ., Angust-platz, D-6500 Mainz, W. Germany
Immunology; 45(1):85-96 1982

C3b receptor protein was purified from human erythrocytes by 2 M KBr solubilization and affinity chromatography on C3-coated sepharose. This material served as antigen for raising monoclonal antibodies. To investigate the distribution and antigenic relationship between the receptors for C3b on human erythrocytes, lymphoid and phagocytic cells, as well as kidney cells three monoclonal antibodies were selected which inhibited the binding of EAC14 23b to complement receptor-bearing cells. This could be shown for human erythrocytes by inhibiting the immune adherence reaction, for tonsil lymphocytes, Raji cells, and guinea-pig spleen cells by inhibition of rosette formation of these cells with EAC14 23b, and for human renal glomeruli by blocking of the adherence of EAC14 23b to kidney sections. In contrast, these monoclonal antibodies were not capable of inhibiting rosette formation of human granulocytes and monocytes with EAC14 23b. The antibodies only interfered with the rosette formation, of EAC14 23bi and

EAC14 23d with Raji cells and tonsil lymphocytes - if at all - at high concentrations, whereas the rosette formation of Raji cells and tonsil lymphocytes with EAC14 23b was influenced by supernatants of the selected clones up to a dilution of 1:10(3) to 1:10(5). (Author abstract) (24 Refs)

177. ABSENCE OF IR GENE CONTROL OF T CELLS RECOGNIZING FOREIGN ANTIGEN IN THE CONTEXT OF ALLOGENEIC MHC MOLECULES.

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Nature; 295(5849):531-533 1982

The possible influence of the immune response (Ir) phenotype of T cells and antigen-presenting cells (APC) on the secondary response in vitro was studied. Antigen poly(Glu40Ala60) (GA) was used as test antigen because the number of responder and nonresponder H-2 haplotypes to this antigen is approx the same. The responses of T cells primed in vitro to GA on syngeneic APC were studied to ascertain that the in vitro system is subject to the same Ir gene control as the in vitro response of T cells primed in vivo. Results indicated that responder T cells can mount a proliferative response when primed with GA on syngeneic APC. T cells from F1 hybrids between responder and nonresponder mice can only respond to GA when presented by F1 APC, or APC of the responder parent. Ir gene control of the in vitro secondary T-cell response was identical to that observed after priming in vivo. Anti-GA response was tested in allogeneic T cell-APC combinations: responder T cell-responder APC, nonresponder T cell-nonresponder APC, nonresponder T cell-responder APC, and responder T cell-nonresponder APC. Results showed that T cell proliferation to GA was readily induced in all four types of strain combination. The response of T cells to antigen presented by fully allogeneic APC is not under Ir gene control. (14 Refs)

178. THE STIMULUS TO HOST CELL PROLIFERATION IN GRAFT-VERSUS-HOST REACTIONS.

Ford WL, Rolstad B, Fossum S, Hunt SV, Smith ME, Sparshott SM

Dept. Pathology, Univ. Medical Sch., Stopford Building, Oxford Road, Manchester M13 9PT, England

Scand J Immunol; 14(6):705-713 1981

Two experiments are described concerned with the mechanism of host cell activation in the rat popliteal lymph node (LN) undergoing a graft-vs-host (GVH) reaction. (1) Irradiated, F1 hybrid hosts (750 rad) mounted an impaired response to parental strain T cells. This was augmented by an intravenous injection of F1 hybrid lymphocytes but not by parental strain B lymphocytes syngeneic with the initiating T cells. When the donor T cells (footpad) and B lymphocytes (intravenous) were completely allogeneic the residual response of the irradiated F1 was completely inhibited. (2) The popliteal LN response in the semi-allogeneic situation of the type (A x C)F1 to (B x C)F1 was, if anything, weaker than in the allogeneic situation AA to BB. These results and other data are discussed in terms of a possible major histocompatibility complex (MHC) requirement for host cell activation. The sharing of an MHC haplotype between donor and host cells is unlikely to be a necessary or sufficient condition for host cell activation. (Author abstract) (43 Refs)

179. THYMIC MEDULLARY LYMPHOCYTES. I. LYMPHOKINES PRODUCED BY THYMIC MEDULLARY LYMPHOCYTES AS A SECOND SIGNAL FOR INTRATHYMIC STEM CELL HOMING.

Papiernik M, Laroche L

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Cell Immunol; 66(2):233-239 1982

Lymphokines produced by thymic medullary cells (TMC) or by normal spleen cells after allogeneic stimulation have been tested for their chemotactic properties in an in vitro migration test. Lymphokines produced by TMC specifically attract cells from nude spleen or from T-cell-deprived spleen depleted of macrophagic cells, but not from normal adult spleen. Supernatants produced by normal adult spleen cells did not attract any of the cells tested (nude spleen cells, T-cell-deprived spleen cells, or normal spleen cells). These results suggest a role for mature TMC in intrathymic stem cell homing. These cells could deliver a second signal to the stem cell, complementary to those provided by thymic epithelium. (Author abstract) (19 Refs)

180. THE AREA OF ATTACHMENT OF CYTOTOXIC T LYMPHOCYTES TO THEIR TARGET CELLS SHOWS HIGH MOTILITY AND POLARIZATION OF ACTIN, BUT NOT MYOSIN.

Ryser JE, Rungger-Brandle E, Chaponnier C, Gabbiani G, Vassalli P

Div. d'Hematologie, Hopital Cantonal, Geneva, 1211, Switzerland

J Immunol; 128(3):1159-1162 1982

Conjugates of cytotoxic T lymphocytes attached to their target cells were studied by double immunofluorescence on fixed smears to detect simultaneously the localization of actin and myosin within the cells. Actin was found to be polarized in the area of attachment of the lymphocytes (but not of the target cells), whereas myosin remained evenly distributed in the cytoplasm. When living conjugates were brought to 37 C to induce cytotoxicity, this pattern remained unchanged, but observation by interference reflection microcinematography revealed a high motility of the lymphocytes in the contact area. This localized motility in the area of attachment associated with a peculiar actin polarization, which has no equivalent in any type of cell contact presently known, could represent a necessary step in the sequence of events leading to target cell killing by cytotoxic T lymphocytes. (Author abstract) (24 Refs)

181. DIFFERENTIAL LYSIS OF ENDOGENOUS AND ACTIVATED NATURAL KILLER CELLS BY ANTI-NK-1.2 ANTIBODY AND COMPLEMENT.

Kumar V, Barnes MC, Bennett M, Burton RC

Dept. Pathology, Boston Univ. Sch. Medicine, Boston, MA, 02118

J Immunol; 128(3):1482-1484 1982

Data indicating that natural killer (NK) cells activated by a variety of agents, including lymphocytic choriomeningitis virus, polyinosinic-polycytidilic acid, and interferon, showed markedly diminished expression of the cell surface NK cell-specific alloantigen NK-1.2, to the point where these cells may be totally resistant to lysis by anti-NK-1.2 serum and complement, are presented. (15 Refs)

CMI METHODOLOGY

182. USE AND ABUSE OF EIGHT WIDELY-USED DIAGNOSTIC PROCEDURES IN CLINICAL IMMUNOLOGY: A WHO MEMORANDUM.

Seligmann M, Bentwich Z, Bianco N, Jager L, Houba V, Lambert PH, Knapp W, Rose N, Thompson R, Torrigiani G, De Weck A
(c/o Chief, Immunology) World Health Organization, 1211 Geneva 27, Switzerland
Bull WHO; 59(5):717-728 1981

Eight widely-used clinical immunologic diagnostic procedures, and indications for their use are reviewed. Methods currently recommended are outlined and their limitations discussed. Tests discussed are quantification of immunoglobulins, immunoelectrophoretic analysis of immunoglobulins in biological fluids, measurements of total and specific IgE, complement measurements, detection of immune-complexes in human biological fluids, autoantibodies by indirect immunofluorescence, B and T cell determination, and lymphocyte response to mitogens in the evaluation of cell-mediated immunity. (5 Refs)

183. ELIMINATION OF T-LYMPHOCYTES FROM HUMAN BONE MARROW WITH MONOCLONAL T-ANTIBODIES AND CYTOLYTIC COMPLEMENT.

Granger S, Janossy G, Francis G, Blacklock H, Poulter LW, Hoffbrand AB
(c/o Janossy) Dept. Immunology, Royal Free Hosp. Sch. Medicine, Pond St., London NW3 2QG, England
Br J Haematol; 50(2):367-374 1982

Complement-mediated cytolysis has been used to remove T-lymphocytes from suspensions of human peripheral blood and bone marrow. Selective T-cell removal was investigated by three monoclonal antibodies, OKT3, MBG6 and OKT11A. All three removed greater than 90% of T-cells but combinations were necessary to kill greater than 99% of T-cells in vitro. The macrophage-granulocyte and erythroid colony forming cells of the bone marrow were spared. The method can be applied on bulk BM samples during clinical BM transplantation and will be useful to establish whether the virtually complete removal of T-lymphocytes totally prevents transplant associated graft-vs-host disease in man. (Author abstract) (21 Refs)

184. A WHOLE-BLOOD TECHNIQUE FOR TESTING PRODUCTION OF HUMAN INTERFERON BY LEUKOCYTES.

Kirchner H, Kleinicke C, Digel W
Institut fur Virusforschung, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
J Immunol Methods; 48(2):213-219 1982

Interferon production was studied in mixtures of whole blood of healthy adults with tissue culture medium. There was no need to supplement the system with additional foreign serum and even the autologous serum could be removed by washing in serum-free medium without impairment of interferon production. Heparinized blood samples could be stored in the refrigerator overnight before performing the assay. In this test, production of interferon gamma was observed in response to phytohemagglutinin, concanavalin A, pokeweed mitogen, staphylococcal enterotoxin A, and to OKT-3, a monoclonal anti-T cell antibody. Production of interferon alpha was observed when viruses were used as inducers. Our experiments show that in the whole-blood assay the responses to several inducers of different types of interferons may be readily monitored under serum-free conditions. We believe that this test will be of value for testing large numbers of normal individuals (for investigations of the genetics of interferon production) or of patients with a variety of diseases. (Author abstract) (11 Refs)

185. ULTRASTRUCTURAL IDENTIFICATION OF NEOPLASTIC HISTIOCYTES-MONOCYTES. AN APPLICATION OF A NEWLY DEVELOPED CYTOCHEMICAL TECHNIQUE.

Kim H, Pangalis GA, Payne BC, Kadin ME, Rappaport H
(c/o Rappaport), City of Hope Natl. Medical Center, Duarte, CA, 91010
Am J Pathol; 106(2):204-223 1982

We applied a newly developed ultrastructural cytochemical technique utilizing 2-naphthyl thiol acetate (NTA) as a substrate in three cases of true histiocytic-monocytic malignancy and three controls. The enzyme 2-naphthyl thiol acetate esterase was identified in both neoplastic and benign histiocytes-monocytes in the form of electron-dense material within the cytoplasm. The NTA esterase varied in size and shape and showed no clear relationship with cytoplasmic organelles. The distribution and pattern of staining were very similar to those of the light-microscopically demonstrated alpha-naphthyl acetate esterase reaction. The main advantages of this method are: (1) histiocytes-monocytes can be identified in the absence of lysosomes or phagocytosis; (2) unequivocal, simultaneous documentation of both histiocytic esterase and subcellular structure is possible; and (3) both blood and solid tissue specimens can be utilized. Our findings demonstrate the usefulness and applicability of ultrastructurally demonstrated NTA esterase in the study of histiocytic-monocytic malignancies. (Author abstract) (39 Refs)

186. MOUSE ERYTHROCYTE FORMATION. A MARKER FOR RESTING B LYMPHOCYTES.

McGraw DJ, Kurec AS, Davey FR
(c/o Davey) Dept. Pathology, State Univ. New York Upstate Medical Center, 750 E. Adams St., Syracuse, NY, 13210
Am J Clin Pathol; 77(2):177-183 1982

The ability of peripheral blood lymphocytes to form rosettes with mouse erythrocytes was examined using lymphocytes from normal healthy individuals of various ages and of neoplastic lymphoid cells from patients with a variety of lymphoproliferative disorders. Our results indicated that only B lymphocytes form mouse rosettes (MR). The percentage of MR varied slightly according to the strain of mouse erythrocytes used in the assay. Little variation in the mean percentage of MR was observed when lymphocytes from various age groups of healthy individuals were studied. When neoplastic lymphoid cells were incubated with mouse erythrocytes only lymphocytes from patients with chronic lymphocytic leukemia formed an increased number of MR. Peripheral blood B lymphocytes lost their ability to form MR following incubation with pokeweed mitogen. These findings supported the view that the determinant on B lymphocytes which binds to mouse erythrocytes was present only at a resting stage of B cell maturation. (Author abstract) (36 Refs)

SUPPRESSOR CELL ACTIVITY

187. INACTIVATION OF STEM CELLS BY ALLOGENEIC LYMPHOCYTES: CHARACTERISTICS OF SUPPRES SOR CELLS BLOCKING THE KILLER EFFECT OF SYNGENEIC LYMPHOCYTES.

Ignat'eva GA, Man'ko VM, Dishkant IP
Moscow, USSR
Tsitologiia; 23(12):1386-1394 1981

Mechanism of interaction of killer and suppressor cells was studied in CBA, C57BL, and (CBA x C57BI)F1 mice. Analysis of inactivating ability of different subpopulations of T-lymphocytes showed that the killer activity of T lymphocytes from the lymph nodes (T-LN) was similar to that of T-lymphocytes from the spleen (T-S) if the total number of transplanted cells did not exceed 5 x 10(5). For larger doses of transplanted cells, the killer activity of T-LN was greater than that of T-S. Index of inactivation of the stem cells after transplantation of a mixture of T-LN and T-S was less than the sum of inactivation indices for T-LN alone and T-S alone. Interaction of T-LN and T-S depended upon the ratio of lymphoid components in the mixture. Antilymphocytic sera inhibited killer cells but did not affect suppressor cells. In vitro experiments showed that killer cells belong to anti-Thy-1-sensitive T-lymphocytes. Suppressor cells were found to be resistant to anti-Thy-1-sera. The spleen cells from thymectomized mice did not exhibit the suppressor activity. Thymectomy did not affect activity of killer cells. (15 Refs) (In RUS)

188. INDUCTION OF T15-SPECIFIC SUPPRESSOR T CELLS IN MICE WITH THE CBA/N DEFECT BY NEONATAL INJECTION WITH ANTI-T15 IDIOTYPE ANTIBODY.

Kim BS, Massey PB
Dept. Microbiology-Immunology, Northwestern Univ., Chicago, IL, 60611
J Immunol; 128(3):1145-1148 1982

Mice with the CBA/N defect (xid) are unresponsive to phosphorylcholine (PC). To determine whether idiotype-specific suppressor T cells can also be generated in these defective mice, defective (CBA/N x BALB/c)F1 male and nondefective (CBA/N x BALB/c)F1 female or (BALB/c x CBA/N)F1 male mice were neonatally injected with antibodies specific for the major idiotype of anti-PC antibody, ie, anti-TEPC-15 idiotype (T15id) antibody. Suppressor cell activity was examined by co-culturing spleen cells from neonatally treated F1 mice with spleen cells of normal nondefective F1 mice in the presence of antigen. Spleen cells from defective (CBA/N x BALB/c)F1 mice treated with anti-T15id antibody demonstrated a level of suppressor activity (greater than 83% suppression) comparable to that of similarly treated nondefective F1 mice. This suppression was specific for the T15id of anti-PC response, and a Lyt-1(-)2-bearing T cell population appeared to be responsible for the active suppression. These suppressor T cells recognized T15 but not PC, based on a functional absorption test. These results indicate that the CBA/N defects, including the deficiency in the anti-PC response by B lymphocytes and a possible T cell defect, do not influence the generation of T15id-specific suppressor T cells by neonatal injection with anti- T15id antibody. (Author abstract) (33 Refs)

189. ACTIVATION OF SUPPRESSOR T CELLS BY AUTOLOGOUS LYMPHOBLASTOID CELLS: A MECHANISM FOR FEEDBACK REGULATION OF IMMUNOGLOBULIN SYNTHESIS.

James SP, Yenokida GG, Graeff AS, Strober W
Immunophysiology Section, Metabolism Branch, NCI, NIH, Bethesda, MD, 20205
J Immunol; 128(3):1149-1154 1982

In this study, the regulatory potential of T cells activated as a result of exposure to autologous lymphoblastoid cells was examined. In initial studies it was observed that the proliferative response of T cells induced by exposure to mitogen-transformed or Epstein Barr virus (EBV)-transformed autologous lymphoblastoid cells was greater than the proliferative response of T cells induced by exposure to unstimulated autologous B cells. Such activated T cells profoundly suppressed pokeweed mitogen (PWM)-stimulated immunoglobulin synthesis by autologous indicator cells, but compared to fresh T cells or cultured T cells, these activated cells had a diminished capacity to provide help for PWM-stimulated immunoglobulin synthesis. In additional studies it was found that (1) both PWM-transformed B cells and EBV-transformed B cells were able to activate suppressor T cells, suggesting that the mechanism of activation is independent of the agent used to transform the lymphoid cells; (2) T cells cultured with PWM-induced lymphoblastoid cells did not suppress immunoglobulin synthesis when added to PWM-stimulated cells after 3 days of culture, indicating that suppression was not due to killing of immunoglobulin-secreting cells; (3) mitogen-induced lymphoblastoid cells acquired maximal ability to activate suppressor T cells after 3 days of culture with the mitogen, indicating that lymphoid cells had to undergo mitogen-induced changes to activate suppressor T cells. These results are compatible with the concept that when B cells are activated to differentiate into immunoglobulin-secreting cells, they express new determinants that are capable of activating suppressor T cells, which can then act to inhibit further B cell differentiation. (Author abstract) (26 Refs)

190. INTERRELATIONSHIP WITH A SUPPRESSOR CHARACTER AMONG THE LYMPHOCYTES OF GUERIN T8 TUMOR CARRIERS IN DIFFERENT EVOLUTIVE STAGES.

Dumitrescu R, Tugearu K
Institutul oncologic, Bucharest, Rumania
Rev Chir [Oncol]; 20(1):17-22 1981

The dialysis chamber method was used to study the effect of suppressor lymphocytes obtained from rats with Guerin T8 tumors (greater than 5 cm in diameter) on the splenic lymphocytes of rats grafted 7, 9, and 11 days previously with small tumors and those grafted 28 days previously which did not develop tumors. A dialyzable factor with a mol wt of less than 10,000 produced suppression. Lymphocytes of rats not bearing tumors had no cytotoxic or suppressor action. (17 Refs) (In RUM)

191. T-CHRONIC LYMPHOCYTIC LEUKAEMIA PRESENTING AS PRIMARY HYPOGAMMAGLOBULINAEMIA - EVIDENCE OF A PROLIFERATION OF T-SUPPRESSOR CELLS.

Thien SL, Catovsky D, Oscier D, Goldman JM, Van Der Reijden HJ, Melief C, Rumke HC, Ten Berge RJ, Von Dem Borne AE

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Clin Exp Immunol; 47(3):670-676 1982

A 63-yr-old man with late onset hypogammaglobulinemia is described. Splenectomy, carried out because of marked splenomegaly and pancytopenia, demonstrated marked T lymphocytic infiltration in the splenic red pulp with prominent germinal centers. A persistent peripheral blood and bone marrow lymphocytosis ensued (10 x 10(9)/l and 40% respectively) and this was consistent with T-chronic lymphocytic leukemia (T-CLL). Over 88% of his blood lymphocytes were E, OKT3, OKT8 and OKT11; 54% of the T lymphocytes had receptors for IgG (Tgamma cells). Functional studies showed that the T lymphocytes of this parent lacked killer and natural killer cell function but they effectively suppressed the differentiation of normal B cells in a PWM stimulated system. It is suggested that the T-CLL in this patient resulted from the proliferation of the T suppressor subset which was responsible for his hypogammaglobulinemia. (Author abstract) (21 Refs)

192. SUPPRESSOR CELLS OF MAN.

Ellner JJ

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Clin Immunol Rev; 1(1):119-214 1981

Human suppressor cells are discussed with respect to T-cell subsets, functional categorization of suppressor T-cells, suppression by macrophages and prostaglandin-secreting suppressor cells, suppressor cells in infectious diseases, autoimmune disease, immunodeficiency diseases and related conditions, and tumors. Suppressor cells favoring tumor growth and those associated with immunodeficiency (T-cell dysfunction in Hodgkin's diseases and other tumors and B-cell dysfunction in multiple myeloma and other tumors) are reviewed. The role of suppressor cells in immunoregulatory tumors is considered. (304 Refs)

193. TUMOUR-INDUCED SPECIFIC SUPPRESSION: A LIMITATION TO IMMUNOTHERAPY.

Scott MT

Dept. Experimental Immunobiology, Wellcome Res. Laboratories, Beckenham, Kent, England

Immunol Today; 3(1):8-9 1982

Response of tumor patients to immunotherapy depends on the competence of the patient's immune system. A tumor evidently produces factors that block effective specific response to tumor cells. Blockage is apparently effected by suppressor T cells induced by the tumor. Studies in mice indicate that tumor regression can be achieved in mice deficient in T cells. Tumor-induced specific immunosuppression may precede generalized immunosuppression appearing in later stages of disease. Response to immunotherap y may be improved by prior removal of the primary tumor, if immune response is restored to near normal. (7 Refs)

OTHER RELATED STUDIES

194. T(15;17) TRANSLOCATION IN ACUTE PROMYELOCYTIC LEUKEMIA (M3) AND CYTOLOGICAL 'M3-VARIANT'.

Berger R, Bernheim A, Daniel MT, Valensi F, Flandrin G

Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies, et les Maladies du Sang Hopital Saint-Louis, 2, place du Dr A-Fournier, F-75475 Paris Cedex 10, France

Nouv Rev Fr Hematol; 23(1):27-38 1981

Of 158 patients with nonlymphoblastic acute leukemia, 20 exhibited the t(15;17) chromosomal translocation. Of these 20 patients, 15 had M3-type acute promyelocytic leukemia (APL); 5 had the chromosomal translocation but did not fit normal cytological criteria for APL (M3-variant: M3var). Patients with M3 APL showed leukopenia or moderate hyperleukocytosis. Patients with M3var had marked hyperleukocytosis. Bone marrow aspirates from M3 patients were characterized by highly granular blast cells with irregular nuclei. 'Faggot cells' containing Auer bodies were found in varying numbers. Some patients had cells with small, single- or bi-lobed nuclei, suggesting different degrees of maturation among blast cells. Blast cells from M3var patients, particularly cells from peripheral blood, were more faintly granular and generally large. Nuclei were irregular and cytoplasm was abundant. The general hematologic picture was similar to acute monocytic leukemia. One M3var patient had cytological characteristics intermediate between the other M3var patients and the M3 patients. M3 cells showed a positive chloroacetate esterase reaction; M3var cells were negative. Results suggest differences in maturation and kinetics of blast cells in M3 and M3var APL. (27 Refs)

195. TUBULIN AS A MAJOR CELL SURFACE PROTEIN IN HUMAN LYMPHOID CELLS OF LEUKEMIC ORIGIN.

Rubin RW, Quillne M, Corcoran JJ, Ganapathi R, Krishan A

Dept. Anatomy (R-124), Univ. Miami Medical Sch., P. O. Box 016960, Miami, FL, 33101

Cancer Res; 42(4):1384-1389 1982

Surface-exposed proteins of vinblastine-sensitive human lymphoid cell line of leukemic origin (CCRF-CEM) were examined by the lactoperoxidase-catalyzed iodination and two-dimensional polyacrylamide gel electrophoresis methods. Spots which comigrate with bovine brain tubulin and rabbit muscle actin were prominently labeled in the whole membrane but not in the high-speed supernatant fraction of the disrupted cells. Mild trypsinization of labeled cells removed the iodinated tubulin and actin without significantly affecting the protein staining pattern. Iodination of normal human lymphocytes resulted in no labeling of the tubulin or actin. The presence of surface-exposed tubulin in this leukemic cell line suggests a possible mechanism for their enhanced sensitivity to the cytotoxic action of vinblastine. (Author abstract) (28 Refs)

196. AN ACTIVATION-INHIBITION MODEL OF CYCLIC GRANULOPOIESIS IN CHRONIC GRANULOCYTIC LEUKEMIA.

MacDonald N

Dept. Natural Philosophy, Univ. Glasgow, Glasgow G12 8QQ, Scotland

Math Biosci; 54(1/2):61-70 1981

An activation-inhibition model of the cyclic granulopoiesis in CGL is presented. In chronic granulocytic leukemia (CGL), granulocyte counts may vary in cycles of 30-70 days, suggesting the operation of a negative feedback control mechanism with a time delay equal to the maturing time of the granulocytes. In the model, mature monocytes are assumed to secrete a stimulating agent and mature granulocytes an inhibiting agent. The inhibiting agent reduces the monocytic production of the stimulating agent. Leukemic granulocytes are assumed to produce less inhibiting agent than normal granulocytes. The long cycles of granulopoiesis in CGL may indicate that the leukemic granulocytes have an abnormally long maturation time. The model predicts that a declining production of inhibiting factor should be less marked when oscillations are present than for typical leukemic granulocytes; the cyclic oscillations of counts are predicted to be accompanied by monocyte oscillations. (21 Refs)

197. ALPHA2HS GLYCOPROTEIN BINDS TO LYMPHOCYTES TRANSFORMED BY EPSTEIN-BARR VIRUS.

Lewis JG, Crosier PS, Andre CM
Dept. Clinical Biochemistry, Christchurch Clinical Sch. Medicine, Christchurch Hosp., Christchurch, New Zealand
FEBS Lett; 138(1):37-39 1982

Binding of alpha2HS glycoprotein to Epstein-Barr virus (EBV)-transformed peripheral blood lymphocytes was studied by indirect immunofluorescence and by direct counts of cell-bound 125I-alpha2HS glycoprotein. This glycoprotein binds appreciably to EBV-transformed, but not to normal autologous, untransformed, lymphocytes (dissociation constant 5.0 x 10(-7) M, with 0.5 x 10(6) sites/cell). Binding of transformed cells is not blocked by deoxyribonuclease pretreatment, but can be partially blocked by ribonuclease or pronase pretreatment. (11 Refs)

198. DEFINITION OF ALIEN H-2 DETERMINANTS ON A FRIEND LEUKEMIA BY ANALYSIS OF ALLOREACTIVITY OF CTL FROM PRIMARY MLC.

Greenberg PD, Cheever MA, Fefer A
Div. Oncology, RK-25, BB 1015 Health Sciences, Univ. Washington, Seattle, WA, 98195
J Immunogenet; 8(6):493-508 1981

An in vivo passaged subline (HFL/d) of Friend virus-induced leukemia of BALB/c origin expressed alien H-2 antigens as determined by reactivity with cytolytic T lymphocytes (CTL). This subline originated from an in vitro passaged subline HFL/d-tc, which when inoculated into BALB/c mice induced weak transplantation resistance. During adaptation to in vivo growth the new ascitic subline HFL/d apparently acquired the capacity to stimulate a cytotoxic response to H-2d antigens, but lost the ability to be lysed by CTL or antisera directed to its H-2d determinants. The presence of H-2d antigen of HFL/d recognizable by CTL was further confirmed by the inhibition of lysis of H-2d targets by HFL/d cold targets. HFL/d stimulated in primary mixed lymphocyte culture (MLC) the generation of CTL which could lyse HFL/d through recognition of non-H-2d determinants not detectable on the parent in vivo passaged subline HFL/d-tc. The alloantigens on HFL/d were typed by generating CTL in primary MLC with HFL/d as stimulator, and measuring reactivity to targets with known H-2 antigens, and was confirmed by assessing recognition of HFL/d targets by CTL generated in primary MLC with stimulators expressing known H-2 antigens. HFL/d expresses Kd and Dd determinants derived from its strain of origin, alien determinants similar to Kb and Db antigens, and at least one additional determinant not present on normal H-2d or H-2b cells. CTL generated in MLC in a sensitive tool for examination of tumors for the presence of alien and/or cross-reactive H-2 determinants. (39 Refs)

199. HUMAN LEUKOCYTE INTERFERON-MEDIATED GRANULOPOIETIC DIFFERENTIATION ARREST AND ITS ABROGATION BY LITHIUM CARBONATE.

Verma DS, Spitzer G, Gutterman JU, Beran M, Zander AR, McCredie KB
Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Hematol; 12(1):39-46 1982

Interferon has been shown to inhibit erythropoietic and granulopoietic differentiation. Since lithium carbonate (Li) elevates granulocyte levels in a variety of neutropenic disorders, we investigated the effect of Li on human leukocyte interferon (HLIF)-mediated inhibition of granulopoietic differentiation. Using an agar culture technique for cloning granulocyte-macrophage progenitor cells (GM-CFC), we demonstrated that Li blocks HLIF-induced granulopoietic differentiation arrest in a dose-dependent manner. Results of removal of T lymphocytes from marrow cells suggest that this Li effect is not mediated through marrow T lymphocytes. (Author abstract) (17 Refs)

200. EXISTENCE OF TARTRATE-RESISTANT ACID PHOSPHATASE ACTIVITY IN DIFFERENTIATED LYMPHOID LEUKEMIC CELLS.

Usui T, Konishi H, Sawada H, Uchino H
First Div. Internal Medicine, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
Am J Hematol; 12(1):47-54 1982

Acid phosphatase (AcP) in neoplastic cells from various lymphoid leukemias was examined. In the cytochemical studies, tartrate-resistant AcP (T-rAcP) activity was observed in the neoplastic cells from well-differentiated lymphoid leukemias such as adult T-cell leukemia (ATL), B-cell chronic lymphocytic leukemia (B-CLL), T-cell chronic lymphocytic leukemia (T-CLL), and hairy-cell leukemia (HCL). T-rAcP activity was also detected in a small number of leukemic cells obtained from T-cell acute lymphoblastic leukemia (T-ALL), while it was not detected in the neoplastic cells from null-ALL, macroglobulinemia, and multiple myeloma (MM). In the electrophoretical studies, fraction 1 (F-1), F-3, F-3b, and F-4 were completely tartrate-sensitive, while F-2 was partially resistant and F-5 was completely resistant. T-rAcP activity (F-5) was observed in ATL cells, B-CLL cells, and HCL cells, while it was not detected in ALL cells, macroglobulinemia cells, and MM cells. The present study indicates that T-rAcP activity is observed not only in HCL cells but also in the well-differentiated lymphoid cells such as ATL cells, B-CLL and T-CLL cells except the most highly differentiated forms of B-cells of MM and macroglobulinemia. (Author abstract) (21 Refs)

201. 5'-NUCLEOTIDASE ACTIVITY IN PERMANENT HUMAN LYMPHOID CELL LINES: IMPLICATION FOR CELL PROLIFERATION AND AGING IN VITRO.

Sun AS, Holland JS, Ohnuma T, Slankard-Chahinian M
Dept. Neoplastic Diseases, Mount Sinai Sch. Medicine, 5th Ave. and East 100th St., New York, NY, 10029
Biochim Biophys Acta; 714(3):530-535 1982

The 5'-Nucleotidase of 11 human lymphoid cell lines was measured. These cell lines were homogeneous B, T and Null cells, had an unlimited lifespan in vitro, and were subcultivated from leukemic cells of patients with Burkitt lymphoma, the blastic phase of chronic myelocytic leukemia, or acute lymphoblastic leukemia. 5'-Nucleotidase activities in normal human lymphocytes and in human fibroblasts (VA-13 and IMR-90) could be determined at a cellular protein concentration as low as 0.025 and 0.007 mg/ml, respectively. In all the 11 lymphoid cell lines, including 8 B-cell lines (RPMI 8422, B46M, RPMI 1788, DAUDI, HRIK, B411-4, B85 and DND-3-9A), 2 T-cell lines (MOLT 3 and RPMI 8402) and 1 Null cell line (NALM-1) 5'-nucleotidase was undetectable with the protein concentration range from 0.033 to 8.543 mg/ml. Previously 5'-nucleotidase activity was found to increase 10-, 6-and 20-fold in normal human embryonic lung (WI-38 and IMR-90 cells) and chick embryo fibroblasts, respectively, from a young rapidly proliferative to a senescent non-proliferative stage. These data demonstrate that the large increase in 5'-nucleotidase activity occurs concomitantly with the in vitro senescence of these normal cell lines. The present study suggests that this large increase in 5'-nucleotidase activity during cell aging is absent in these permanent lymphoid cell lines. The undetectable 5'-nucleotidase activity may be a biochemical characteristic of these homogeneous B, T and Null cells originating from the aforesaid leukemias. The implications of these results for cell proliferation and aging are discussed. (Author abstract) (28 Refs)

202. MEMBRANE-BOUND AND CELLULAR IMMUNOGLOBULINS IN HUMAN B-LYMPHOMA LINES AND DERIVED HYBRIDS.

Spira G, Aman P, Silvian I, Koide N, Ber R, Klein G
Faculty Medicine, Technion, P.O.B. 9649, Haifa, 31096, Israel
Immunobiology; 160(3/4):340-351 1981

Hybrids derived from the fusion of cell lines representing different maturation stages were studied for their membrane and cellular immunoglobulin expression. The hybrids can be subdivided into three groups, with one common parental line in each group. In the first group, Raji cells represent the common parent: it contains small amounts of membrane and cytoplasmic mu and kappa chains. In the second group, PUT is the common parent, an ouabain and TG-resistant subline of the BL-derived P3HR-1 line. PUT contains a truncated intracellular mu chain. The third group consists of hybrids between K562, an EBV-negative human erythroleukemia line and two different BL lines. Membrane-immunoglobulin expression was intermediate between the parental lines in the first two groups derived from the fusion of two BL lines. In the third group, hybridization with the K562 cell suppressed the membrane-Ig expression of the B-cell partner. Total cellular immunoglobulin determinations showed that some cells synthesized light chains in excess of heavy chains, others contained an excess of heavy chains, while still others had equal amounts of heavy and light chains. The hybrids showed a variety of patterns, including amplification of the parental phenotypes, appearance of new phenotypic combinations, and eclipse of one or both parental phenotypes. A comparison of the total and the membrane-associated immunoglobulin patterns suggests independent handling of intracellular and membrane immunoglobulin synthesis. (Author abstract) (28 Refs)

203. ANALYSIS OF THE FATE OF SYSTEMICALLY ADMINISTERED LIPOSOMES AND IMPLICATIONS FOR THEIR USE IN DRUG DELIVERY.

Poste G, Bucana C, Raz A, Bugelski P, Kirsh R, Fidler IJ
Smith Kline and French Lab., Philadelphia, PA, 19101
Cancer Res; 42(4):1412-1422 1982

Functional and ultrastructural studies of liposomes injected iv into inbred C57BL/6N mice were performed to determine whether free liposomes can traverse capillaries. In the liver and spleen, organs with discontinuous (sinusoidal) capillaries, ultrastructural and cell fractionation studies revealed that small (300-to 800-A diameter), sonicated, unilamellar liposomes were more efficient in penetrating liver sinusoids to interact with hepatocytes than were large (0.5-to 10-um) multilamellar liposomes. Ultrastructural studies of the behavior of liposomes in the continuous capillaries of the lungs revealed that circulating phagocytic cells engulf the liposomes in the capillaries. Transcapillary migration of free liposomes was not observed. We conclude that free liposomes are unable to extravasate to reach the alveoli for subsequent engulfment by alveolar macrophages. Instead, liposomes in the lung capillaries are engulfed by circulating blood phagocytes which subsequently migrate to the alveoli to become alveolar macrophages. Experiments on the recruitment of blood monocytes into the lungs subjected to whole- or partial-body x-radiation confirmed that transfer of iv-injected liposomes to the alveolar compartment was mediated by blood monocytes. The inability of liposomes to escape from continuous capillaries and their rapid uptake by circulating and fixed phagocytic cells calls into question the feasibility of using liposomes to 'target' drugs to cells in extravascular tissues. (Author abstract) (45 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abramowitz A 53
Ada GL 106
Adenis L 9
Adler WH 99
Advani SH 28
Ahmad R 52
Allardyce RA 93
Allen DJ 50
Alonso G 68
Aman P 202
Amoruso MA 147
Anderson DW 114
Anderson WL 60
Andersson U 49
Andre CM 197
Archer DL 123
Archer MC 6
Arlen M 20
Arnaud M 134
Arrick BA 135
Badea E 105
Bailey DW 81
Bakenhaster K 101
Baldwin RW 54
Ball ED 29
Balls M 63
Bankhurst AD 48
Baral E 15
Barboni F 122
Barnes MC 181
Barrett DS 41
Bartlett SP 103
Battelli MG 122
Begemann M 17
Bell PA 172
Belokhvostov AS 67
Bendtzen K 125
Bennett M 181
Bentwich Z 182
Ber R 202
Beran M 199
Bercsenyi K 121
Berd D 145
Berger R 194
Berman B 55
Bernheim A 194
Berstein LM 12
Beuscart R 9
Bhattacharya A 131
Bianco N 182
Birmingham JR 152
Bischoff P 111
Blacklock H 183
Blakley BR 123
Blattner WA 1
Blomgren H 15
Bobrov YF 12
Boes J 81
Bonneterre J 9
Bonoldi A 56
Bonventre PF 74
Brambilla P 151
Brassil DN 10
Brenan M 165
Brent L 41
Brodarec I 8
Brown R 157
Bruce WR 6
Brunda MJ 128
Brunning RD 35
Bryant SM 150
Bubel HC 74
Bucana C 203
Bucci M 22
Bugelski P 203
Bulic N 14
Burakoff S 132
Burger R 176
Burton RC 103
Burton RC 181
Buslaeva VP 12
Canfield L 94
Capron A 9
Castes M 143
Catovsky D 191
Cenci M 122
Centurioni R 34
Chaponnier C 180
Cheever MA 198
Chekanova IuI 75
Chen KM 23
Chesnut RW 152
Chiricolo M 122
Chiu H 108
Chu AC 21
Chu AC 44
Claas G 17
Clerici E 19
Cohen M 20
Cohn ZA 135
Collins RD 27
Cook JL 95
Corcoran JJ 195
Corneci I 105
Crivii MS 112
Crosier PS 197
Crowther D 38
Czitrom AA 162
Daniel MT 194
Dardenne M 77
Davey FR 186
De Bernardo E 86
De Gast GC 170
De Weck A 182
De Weger RA 36
Degliantoni G 45
Desai PR 13
Dierich MP 176
Digel W 184
Dilman VM 12
Dionigi P 56
Dionigi R 56
Dishkant IP 187
Dorf ME 131
Dray S 57
Drexhage HA 160
Drummond HE 69
Dumitrescu R 190
Dumitrescu R 89
Dygai AM 175
Ehlen T 176
Ehrke MJ 121
Eibl MM 52
Elfenbein GJ 3
Ellner JJ 192
Epstein MA 50
Erba E 134
Faanes RB 109
Falke H 17
Fanciulli F 34
Fanger MW 29
Farrar J 168
Farrar JJ 118
Faulconer RJ 10
Fedorov SN 12
Fefer A 198
Feldbush T 94
Feldman M 85
Fergin PE 44
Ferguson A 69
Ferrone S 149
Feucht H 24
Fidler IJ 203
Fidler IJ 83
Fierz W 165
Filippeschi S 134
Finberg RW 132
Fitzharris P 47
Flandrin G 194
Flexner JM 27
Flier VD 160
Ford WL 178
Fossum S 178
Foucar K 35
Franceschi C 122
Francis G 183
Frankfort HM 55
Frassoni F 96
Fraumeni JF 1
Fritze D 39
Frizzera G 35
Froelich CJ 48
Fry WA 13
Funcini M 45
Gabbiani G 180
Gaist G 22
Galatiuc C 102
Gallagher P 5
Gallagher P 7
Gallo RC 117
Ganapathi R 195
Gangal SG 28
Garattini S 134
Garrone GO 11
Germain RN 131
Gershon RK 167
Gherman M 102
Goedert JJ 1

Gol'dberg ED 175
Goldman CK 3
Goldman JM 191
Goldstein BD 147
Goldstein G 37
Goldstein G 76
Goodman MG 61
Gorczynski RM 84
Gordon J 85
Gottesman SR 139
Graeff AS 189
Graham-Brown RA 37
Granger S 183
Green B 100
Greenberg PD 198
Greenberg SB 129
Greene MH 1
Greene MI 132
Grey HM 152
Griffith OW 135
Grikurova NK 67
Grimm EA 40
Gupta SK 97
Gutterman JU 199
Halliday WJ 79
Halper JP 46
Hamaoka T 168
Hanna N 66
Hasek M 120
Haskill S 146
Hawrylko E 72
Hawrylko E 73
Hayward A 114
Herberman RB 102
Herberman RB. 127
Herberman RB 26
Herberman RD 128
Hersh EM 142
Hilfiker M 168
Hilfiker ML 118
Hill HR 150
Hirata H 107
Hirokawa K 82
Hiserodt JC 163
Hobbs DS 127
Hoffbrand AB 183
Holan V 120
Holden HT 128
Holden HT 85
Holland JS 201
Hollinshead A 20
Horak I 173
Houba V 182
Howard M 168
Hrsak KM 14
Huberman HS 104
Hudson L 30
Hudson L 31
Huhn D 24
Hunt SV 178
Ignat'eva GA 187
Ikic D 8
Imanishi J 130
Ip C 87
Ip MM 87
Irimajiri N 4
Isakson PC 166
Ishii N 177
Jager L 182
James SP 189
Janossy G 183
Janossy G 37
Jarrett O 96
Jensenius JC 31
Johnson B 168
Johnstone AP 30
Johnstone AP 31
Jones C 114
Jones CN 172
Jusic D 8
Kadin ME 185
Kadushin JM 29
Kahn LB 18
Kaieda T 115
Kaiserlian D 77
Kalafut F 91
Kalra DS 97
Kappler JW 152
Kass L 33
Katelan M 14
Katsumoto T 158
Katz DR 162
Kaufman S 110
Kaufmann M 39
Kaufmann SH 169
Kelley S 108
Kennard J 174
Kerman RH 140
Khare AG 28
Kharole MU 97
Kim BS 188
Kim H 185
Kim U 87
Kimura K 4
Kirchner H 184
Kirsh R 203
Kishida T 130
Kishimoto T 115
Kita M 130
Klein G 202
Klein J 177
Klein PA 64
Kleinicke C 184
Klenner D 173
Knapp W 182
Knezevic M 8
Knezevic-Krivak 8
Knight RA 47
Knowles DM 46
Knox SJ 51
Koga Y 161
Kohl S 129
Koide N 202
Kondratjev VB 12
Konishi H 200
Koppi TA 79
Korsmeyer SJ 3
Koudstaal J 16
Kraaijenhagen R 170
Krammer PH 166
Krishan A 195
Krusic J 8
Kubo C 161
Kubo R 152
Kubovic M 14
Kumar V 181
Kundin WD 20
Kung HF 127
Kung PC 37
Kurashige S 156
Kurec AS 186
Lambert PH 182
Laroche L 179
Lau CY 76
Lee SH 108
Lens JW 160
Leoni P 34
Lespinats G 143
Leung KH 121
Leung KN 106
Levine PH 164
Levy R 171
Lewis AM 95
Lewis JG 197
Licastro F 122
Lindsay VJ 93
Lipkin M 6
Lipoldova M 120
Liu JJ 78
Livni N 53
Loo LS 129
Loveland BE 70
Lubaroff DM 94
Lubbe FH 133
Lynch NR 143
MacDonald DM 21
MacDonald DM 44
MacDonald N 196
MacRae S 84
Mackenzie CG 154
Mage M 119
Makinodan T 82
Man'ko VM 187
Manciulea M 102
Mangoni L 45
Manhalter JW 52
Mann DL 1
Manna A 45
Mantovani A 127
Mantovani A 134
Maricic Z 8
Marocchi A 151
Marrack P 152
Marshall SL 3
Martin RR 153
Martinac P 14
Masserini C 19
Massey PB 188
Mastrangelo MJ 145
Matheson DS 100
Mathieson B 119
Matsumoto S 23
Maugaras M 111
Mazumder A 40
McCredie KB 199
McElligott D 94
McGeorge MB 32
McGraw DJ 186
McKenna RW 35
McKenzie IF 70
McLemore TL 153
Mele CA 73
Melief CJ 191

Melief CJ 81
Melik-Gaikarian 175
Melvold RW 81
Merluzzi VJ 109
Meruelo D 174
Michael JG 74
Mickey MR 164
Mier JW 117
Mignot MH 160
Mihich E 121
Millard RE 30
Millard RE 31
Mitsuhashi S 156
Mizutani A 124
Mocarelli P 151
Modai D 110
Mohanakumar T 32
Mokyr MB 57
Montesano R 6
Montrillo M 34
Montroni M 34
Moore M 5
Moore M 7
Morag A 53
Morasca L 134
Morgan EW 21
Moss DJ 50
Mowat AM 69
Mullbacher A 165
Muraguchi A 115
Murgita RA 116
Murray C 1
Murthy SM 13
Mussel HH 176
Nagle LS 126
Nagy ZA 177
Nakagawa T 115
Nakamura H 80
Nathan CF 135
Naylor PH 87
Nazari S 56
Nehlsen-Cannare 138
Neighbour PA 104
Nemirovsky VS 12
Neubauer RH 171
Neuland CY 1
Neville ME 163
Ng AK 149
Nickol AD 74
Nieminen P 98
Nigro ND 6
Niitani H 4
Nikiforov YF 12
Nola P 8
Nomoto K 161
Nordan R 71
Nordlicht N 6
Nossal GJ 62
Novogrodsky A 144
Novotna L 91
Ogino K 23
Ohnuma T 201
Okamoto M 2
Okazaki T 23
Olezza S 56
Onions D 96
Ono S 80
Oort J 160
Oppenheim JJ 119
Opremcak EM 101
Orbach-Arbouys 143
Ortaldo JR 127
Oscier D 191
Ostroumova MN 12
Oth D 111
Ozaki A 4
Paasivuo R 98
Padovan I 8
Padovani R 22
Palacios R 113
Palacios R 49
Pallenzona D 122
Pangalis GA 185
Papiernik M 179
Parente R 22
Path MR 37
Patt YZ 141
Patya M 144
Paul WE 168
Payne BC 185
Peck AB 116
Peiper SC 18
Peller S 110
Peri G 134
Pero RW 159
Pessina A 151
Pestka S 127
Peters H 176
Petrini B 15
Pogosiants EE 65
Popp I 89
Poppema S 16
Poroshina TE 12
Poste G 203
Poste G 83
Poulter LW 183
Price NM 25
Pure E 166
Quddus FF 169
Quillne M 195
Rabin H 171
Rappaport H 185
Ratnofsky S 132
Ravid Z 53
Rayfield LS 41
Raz A 203
Reid JW 10
Renner D 24
Reynolds CW 94
Riabova LV 75
Rickinson AB 50
Rieber EP 24
Rieber M 68
Riethmuller G 24
Rijksen G 170
Rodkey LS 137
Rodrigues D 71
Roe GM 90
Rolstad B 178
Rose N 182
Rosenberg SA 40
Rosenblatt LS 51
Rovini D 19
Rowe M 50
Rozescu B 105
Ruben LN 63
Rubin AL 144
Rubin RW 195
Rudolf M 14
Ruiz P 43
Rumke HC 191
Rungger-Brandle 180
Russell EC 32
Russo C 149
Ryser JE 180
Saad FA 11
Sadi A 11
Saijo N 4
Saksela E 98
Salvi A 34
Santoro F 9
Santos GW 3
Sato K 82
Sawada H 200
Sawyer RT 148
Scanlon EF 13
Schacter B 29
Scheiner O 176
Schellhammer PF 10
Scherrer J 20
Schimpl A 173
Schipper-Kester 170
Schlimok G 24
Schmidtke JR 155
Schmitt M 176
Schofield PF 5
Schofield PF 7
Schwartz A 167
Scornik JC 43
Scott MT 193
Segal S 85
Segre D 78
Segre M 78
Seig SM 10
Seleznev IK 12
Seligmann M 182
Semiglazov VF 12
Servadei F 22
Shadduck RK 126
Shaked U 110
Shaper JH 169
Shea W 87
Shifrine M 51
Shimizu E 4
Shimizu N 23
Silvian I 202
Simpson E 165
Siraganian RP 119
Sjogren HO 159
Slankard-Chahin 201
Smith ME 178
Smith TJ 88
Soimakallio S 92
Soos E 8
Spagnolli F 22
Sparshott SM 178
Spira G 202
Spitzer G 199
Spreafico F 134
Springer GF 13
Springer TA 131
Staal GE 170
Stadler BM 119

Stebbing N 108
Stein RS 27
Steiner L 22
Stenzel KH 144
Stephenson K 126
Stolk JG 160
Strausbach PH 148
Strender LE 15
Strnad BC 171
Strobel S 69
Strober W 189
Strong DM 1
Stukart MJ 81
Stutman O 59
Stutman O 73
Sugarbaker PH 88
Sulica A 102
Sun AS 201
Sunshine GH 162
Susskind BM 109
Sutton SL 167
Sy MS 132
Syrjanen KJ 92
Tabacchi P 122
Tai AS 48
Takaoki M 132
Takasugi M 164
Takatsu K 168
Takizawa T 4
Talmage DW 154
Taniguchi K 161
Tanner K 20
Taradi M 42
Tegtmeyer H 13
Ten Berge RJ 191
Teramoto S 23
Testa N 96
Thiel E 24
Thien SL 191
Thomas JA 37
Thompson R 182
Tibaldeschi C 56
Timens W 16
Ting CC 71
Tomasi TB 60
Toonstra J 36
Torrigiani G 182
Toth S 96
Trepke S 176
Tsyrlina EV 12
Tugearu 89
Tugearu K 190
Uchino H 200
Umezawa H 136
Usui T 200
Valensi F 194
Valentova N 91
Vallera DA 155
Van Der Reijden 191
Van Unnik JA 36
Van der Putte S 36
Varesio L 128
Vasilyeva IA 12
Vassalli P 180
Venitt S 6
Verma DS 199
Villa ML 19
Villa S 151
Vitetta ES 166
Volkman A 148
Von Blomberg BM 160
Von Dem Borne A 191
Vos A 81
Vose BM 5
Vose BM 7
Wada T 23
Wagner DA 87
Waheed A 126
Waldmann TA 3
Walford RL 139
Wallace LE 50
Wallen WC 1
Wang EY 76
Warner NL 48
Wasserman J 15
Waters H 58
Wattre P 9
Waynforth HB 90
Wecker E 173
Weigle WO 61
Weindruch R 139
Weissgarten J 110
Whisler RL 101
Wigzell H 116
Wilkins TD 6
Wilson RW 100
Wing EJ 126
Witz G 147
Wogan GN 6
Wolman M 157
Wright GL 10
Yamamoto H 124
Yamamura Y 115
Yamashita U 80
Yanagihara RH 99
Yenokida GG 189
Yonemoto R 20
Yoshizaki K 115
Zaalberg OB 133
Zadrazil S 120
Zander AR 199
Zhang HZ 40
Zhang YH 149
Zielinski CC 52
Zimmer G 176

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In this issue:

- **EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS** 1-42
- **EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS** 43-69
- **EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION** 70-91
- **THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE** 92-113
- **RELATED BIOLOGY OF IMMUNE CELLS** 114-124
- **CMI METHODOLOGY** 125-128
- **SUPPRESSOR CELL ACTIVITY** 129-133

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. EFFECT OF INDUCTION RADIOTHERAPY-CHEMOTHERAPY AND SPLENECTOMY ON LYMPHOID SUBCLONES IN PATIENTS AFFECTED WITH HODGKIN'S LYMPHOMA IN COMPLETE REMISSION.

Leoni P, Montroni M, Montillo M, Salvi A, Centurioni R, Fanciulli F
Istituto di Patologia Speciale Medica e Metodologia Clinica, Universita di Ancona, Ancona, Italy
G Clin Med; 62(10):685-692 1981

Forty-nine patients with Hodgkin's lymphoma had complete staging, together with determination of T, B, and total lymphocytes. Such evaluations were made at the time of diagnosis,

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HE 20.3173/2:

after induction therapy, approx 1 yr later (36/49), 2 yr later (23/49), and 3 yr later (17/49). Laparotomy and splenectomy were performed on 27 of the patients. According to clinical or pathological staging, three patients were Stage I, 25 were Stage II, 15 were Stage III, and 6 were Stage IV. Symptoms were present in 19 of the patients and absent in 30. Histologic types included nodular sclerosis (31), mixed cellularity (8), lymphocyte depletion (5), and lymphocyte prevalence (3). Treatment consisted of radiotherapy and chemotherapy MOPP (mustine, oncovin, prednisone, and procarbazine). No maintainance therapy was administered. Basic immunological deficits of the patients were worsened by the induction therapy. Total and T lymphocyte values recovered after 2 yr and, after 3 yr, were above basic values. B lymphocyte values were somewhat depressed by the induction therapy but recovered rapidly. Except for the T lymphocyte values, lymphocyte values of the patients that underwent splenectomy were always above those of the non-splenectomized patients. (14 Refs) (In ITA)

2. IMMUNOLOGICAL DATA IN THE CLINICAL EVALUATION OF HODGKIN'S DISEASE.

Burchardt K
Klinika Hematologii, ul. Szkolna 8/12, 60-967 Poznan/VR, Poland
Z Gesamte Inn Med; 36(21):840-842 1981

Pattern of immunological alterations was analyzed in 87 adult patients with Hodgkin's disease. Diagnosis was based on clinical diagnosis and confirmed by lymph node biopsy. Clinical data compared with healthy controls are presented. A decrease in total lymphocyte counts and a diminished count of T-lymphocytes were observed in patients with advanced stages of the disease or in those with radio- or chemotherapeutically induced remissions. Lymphocyte transformation and reactions in skin tests were influenced by the stage of the disease. The cells were below the critical number (500/cubic mm) in the peripheral blood, and inhibition of T-cell function occurred. (21 Refs) (In GER)

3. INCREASED SENSITIVITY OF T CELLS TO REGULATION BY NORMAL SUPPRESSOR CELLS PERSISTS IN LONG-TERM SURVIVORS WITH HODGKIN'S DISEASE.

Vanhaelen CP, Fisher RI
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Am J Med; 72(3):385-390 1982

We have studied the function of T cells in the peripheral blood obtained from long term survivors with Hodgkin's disease in order to determine the sensitivity of those T cells to normal suppressor cell immunoregulatory mechanisms. Concanavalin A-activated suppressor cells from normal donors suppressed the proliferation of lymphocytes obtained from 11 patients (56.8 +-3.5%) and from 28 allogeneic normal control subjects (39.8 +-2.7% [p less than 0.001]). When suppressor monocytes from the normal donors were studied, the mean proliferation of lymphocytes from 19 patients was suppressed 76.3 +-4.8% whereas proliferation of lymphocytes from 26 normal donors was suppressed 46.6 +-4.4% (p less than 0.0001). There was no tendency for the increased sensitivity to suppression that was observed in either assay system to return to normal as the patients' disease free interval increased from 1.5 yr to 12 yr. Furthermore, long-term survivors with diffuse histiocytic lymphoma, who had been treated with comparable chemotherapy, had normal sensitivity to the suppressor monocytes (45.1 +-3.8%). In Hodgkin's disease, the persistent increased sensitivity of T cells to two different normal immunoregulatory cells suggests that the response of the T cell to regulatory signals may be an important cause of the depressed cellular immunity observed in Hodgkin's disease and a clue to the etiology of the disease. (Author abstract) (21 Refs)

4. IMMUNOLOGICAL CHARACTERIZATION OF NON-HODGKIN'S LYMPHOMA: ENRICHMENT OF NEOPLASTIC CELLS FROM LYMPHOID TISSUES AND BLOOD.

Bom-Van Noorloos AA, Van Beek AA, Ubels-Postma J, Zeijlemaker WP, Van Heerde P, Von Dem Borne AE, Cleton FJ, Melief CJ
(c/o Melief), Central Lab. Netherlands Red Cross Blood Transfusion Service, P. O. Box 9190, 1006 AD Amsterdam, The Netherlands
Cancer; 49(8):1605-1612 1982

Cell suspensions prepared from lymph nodes, spleen or peripheral blood of patients with non-Hodgkin's lymphoma (NHL) often contain a high percentage of residual nonmalignant cellular elements. By E-rosette sedimentation, it was possible to enrich such suspensions from patients with various types of lymphoma for malignant cells. In patients with a B- or non-B/non-T-cell lymphoma, the neoplastic cells were found in the non-T fraction. The capacity to respond to stimulation by various stimuli was then confined to the T-cell fraction, which contained the residual normal T-cells. In patients with T-cell lymphomas, in which the malignant cells had retained the capacity to form E-rosettes, lymphoma cells were found in the T fraction. These cells usually did not respond to mitogenic stimuli. Using this separation method, small proportions of neoplastic cells could be identified in mixed cell populations. Thus, in the blood from 9 out of 23 lymphoma patients without abnormalities in routine blood tests, a population of abnormal cells was detected after cell separation. This included a monoclonal B-cell population in the blood of four patients, a questionably monoclonal B-cell population in the blood of two patients and an increased non-B/non-T cell population in the blood of three patients. (Author abstract) (35 Refs)

5. EFFECT OF ESTROGEN ON THE MIXED LYMPHOCYTE REACTION IN NORMAL INDIVIDUALS AND PROSTATIC CANCER PATIENTS.

Herr HW
Urologic Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Prostate; 3(1):17-21 1982

The effect of diethylstilbestrol diphosphate (DES-P) on the normal human mixed lymphocyte reaction (MLR) and on the MLR of patients with advanced prostatic cancer before and during treatment with DES-P was investigated. Peripheral blood lymphocytes were obtained from three healthy volunteers (26-38 yr old) and 72 different pairs of MLR were prepared in triplicate. MLR were also determined in 12 patients (mean age 64) with metastatic prostatic cancer before treatment and 1 hr after treatment with iv infusion of DES-P (1 g/day) for 5 consecutive days. Three patients received DES-P as primary treatment, three after relapse to orchiectomy, and six after relapse to oral estrogen therapy (DES for 9-15 mo at 3-5 mg/day). DES-P was given over a 30 min period and MLR was performed 1 hr after completion of daily infusion. MLR were significantly depressed in prostatic cancer patients (mean 2.6 x 10(-3) nanocpm) in all three groups compared to normals (mean 6.5 x 10(-3) nanocpm). MLR was not more depressed in patients who relapsed while on oral estrogens compared with those who relapsed after orchiectomy or in those with no prior estrogen exposure. Further suppression of the MLR was not observed in any patient group during the 5 days of DES-P therapy. Thus, while the normal MLR was suppressed by high concentrations (2,000 ug/ml) of estrogens in vitro, low levels (less than 100 ug/ml) of DES-P were not suppressive. (6 Refs)

6. CELLS BEARING FC RECEPTORS IN HUMAN MALIGNANT SOLID TUMOURS.

Svennevig JL, Andersson TR
Dept. Surgery, Rikshospitalet, Oslo, Norway
Br J Cancer; 45(2):201-208 1982

Fc-receptor-bearing cells forming EA rosettes with antibody-coated human erythrocytes (Ripley) were studied in cell suspensions and in purified preparations of mononuclear cells (MC) from 20 human malignant tumors. The EA rosettes were studied in preparations made by cytocentrifugation and the rosette-forming cells identified by their nonspecific-esterase activity and phagocytic capacity. Fc receptors were found on 16 +-20% of all cells in the primary cell suspensions. Significantly more tumor-infiltrating lymphocytes had detectable Fc receptors (33 +-18%) than did peripheral-blood lymphocytes in cancer patients (19 +-8%) and normal control subjects (14 +-6%). There was a significant correlation between the proportion of lymphocytes lacking T and B markers (null cells) and the proportion of lymphocytes with Fc receptors. Fc receptors were also found on most tumor-infiltrating macrophages, on some T lymphocytes and polymorphonuclear cells and on a smaller percentage of the tumor cells. The significance of the Fc receptor and its usefulness as a marker of 'host infiltration' into the tumors is discussed. (Author abstract) (29 Refs)

7. LYMPHORETICULAR CELLS IN HUMAN BRAIN TUMOURS AND IN NORMAL BRAIN.

Phillips JP, Eremin O, Anderson JR
Dept. Neurosurgery, St. Laurence's Hosp., Dublin 7, Ireland
Br J Cancer; 45(1):61-69 1982

The present investigation, using various rosetting assays of cell suspensions prepared by mechanical disaggregation or collagenase digestion, demonstrated lymphoreticular cells in human normal brain (cerebral cortex and cerebellum) and in malignant brain tumors. The study revealed T and B lymphocytes and their subsets (bearing receptors for Fc(IgG) and C3) in 5/14 glioma suspensions, comprising less than 15% of the cell population. Between 20-60% of cells in tumor suspensions morphologically resembled macrophages and less than or equal to 75% of these cells formed strong rosettes. Lymphocytes were not found in cancer-free (putatively normal) brain. Macrophages and the smaller 'microglial cells' (both phagocytic, staining with sudan black, and expressing Fc(IgG) and C3 receptors) were found in normal brain in numbers similar to those in tumor suspensions, but with less rosetting avidity. These cells may be part of an immunological defense mechanism. (Author abstract) (34 Refs)

8. IDENTIFICATION OF HUMAN THYMIC EPITHELIAL CELLS WITH ANTIBODIES TO THYMOSIN ALPHA IN MYASTHENIA GRAVIS.

Dalakas MC, Engel WK, McClure JE, Goldstein AL, Askanas V
NIH, Building 36, Room 5D06, Bethesda, MD, 20205
Ann NY Acad Sci; 377:477-485 1981

Thymosin-alpha1 (alpha1) is a potent thymic polypeptide hormone. Using anti-alpha1 antibodies, we applied indirect immunofluorescence to human normal thymus of different ages and to hyperplastic, thymomatous, and 'involuted' thymus of myasthenia gravis (MG) patients. Alpha1 was localized only in the epithelial cells, lying singly, grouped, in Hassell's corpuscles, and proliferated in thymomas. Whereas normal thymuses had fewer and weakly stained cells, MG thymuses had many strongly positive epithelial cells; this was more evident in thymomas. Germinal centers were unstained. 'Involuted' MG thymuses had small islands of brightly stained cells lying among the fatty tissue. In cultured thymuses from three MG patients, epithelial cells but not fibroblasts were brightly stained for alpha1. Our findings (a) demonstrate the location, and presumably the origin, of alpha1 to be the thymic epithelial cell; (b) suggest the possibility that excess alpha1, because of its known effect on T-lymphocyte maturation and transformation of precursors to helper T-cells, may act pathologically to facilitate and perpetuate the dysimmune mechanism in MG; (c) may partially explain the beneficial effect of thymectomy in MG patients of any age; and (d) indicate that epithelial cells may be autonomous for the production of alpha1 as evidenced by their alpha1-positivity in culture. (Author abstract) (36 Refs)

9. ANTI-ACETYLCHOLINE RECEPTOR ANTIBODY SYNTHESIS BY CULTURED LYMPHOCYTES IN MYASTHENIA GRAVIS: THYMIC AND PERIPHERAL BLOOD CELL INTERACTIONS.

Newsom-Davis J, Willcox N, Scadding G, Calder L, Vincent A, Appel SH, Kelly RB, Tindall RS, Koriyama K
Dept. Neurological Science, Royal Free Hosp. Sch. Medicine, London NW3 2QG, England
Ann NY Acad Sci; 377:393-402 1981

Thymus lymphocytes from myasthenia gravis (MG) patients produced anti-acetylcholine receptor (AChR) antibody in culture. Thymic cells from 10 thymoma patients with MG showed no evidence of anti-AChR production. Peripheral blood lymphocytes (PBL) from MG patients, including one of three thymoma patients, also produced anti-AChR in culture. Coculture of autologous thymic lymphocytes and PBL indicated that thymus cells can enhance anti-AChR production by PBL. Characteristics of the antibody production suggest that both antigen presenting cells and AChR-specific helper T-cells may be involved in mediating the enhancing effects of autologous thymic cells on the production of anti-AChR by PBL. (22 Refs)

10. GASTRECTOMY COMBINED WITH SPLENECTOMY AND IMMUNOTHERAPY FOR ADVANCED GASTRIC CANCER PATIENTS.

Miwa H; Kojima K, Tsurumi T, Orita K
First Dept. Surgery, Okayama Univ. Sch. Medicine, Okayama, Japan
Nippon Gan Chiryo Gakkai Shi; 16(7):1365-1370 1981

Postoperative cellular immunity and prognosis of 60 advanced gastric cancer patients (Group A) who were treated with gastrectomy combined with splenectomy were compared with those of 81 such patients (Group B) who were treated with gastrectomy alone. According to stage, 43 Group A and 74 Group B patients had Stage III cancer, and 17 Group A and 7 Group B patients had Stage IV. The splenectomies were performed because of the presence of metastatic lymph nodes and serosal invasion that was discovered during the surgery. Immunotherapy using levamisole (LMS; 150 mg/day, 3 days, po) was given to 18/60 patients who underwent splenectomy. Cellular immunity was investigated using blastogenic response of peripheral blood to phytohemagglutinin (PHA), peripheral lymphocyte counts, and skin responses to purified protein derivative or PHA. Lymph node metastases, particularly of the Number 10 lymph nodes, were more frequent in the Group A patients than in the Group B. Cellular immunity after surgery, compared to that before, decreased in the Group A patients who were not administered the LMS, but increased in the Group A patients who were administered the LMS. Three-yr actuarial survival rate of the Group A patients was 15% less than that of the Group B patients, but the Group A patients had more advanced gastric cancers than the Group B patients. Group A patients who were also administered immunotherapy had survival rates approaching those of the Group B patients. Splenectomy, combined with immunotherapy using LMS or some other drug, should be performed in patients with advanced gastric cancer if lymph node (Number 10 or 11) metastasis or serosal invasion is observed. (17 Refs) (In JPN)

11. IN VITRO REGULATION OF IMMUNOGLOBULIN SYNTHESIS AFTER HUMAN MARROW TRANSPLANTATION. II. DEFICIENT T AND NON-T LYMPHOCYTE FUNCTION WITHIN 3-4 MONTHS OF ALLOGENEIC, SYNGENEIC, OR AUTOLOGOUS MARROW GRAFTING FOR HEMATOLOGIC MALIGNANCY.

Witherspoon RP, Lum LG, Storb R, Thomas ED
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Blood; 59(4):844-850 1982

Immunoglobulin secretion was studied in 37 patients between 19 and 106 days after allogeneic HLA-identical (30 patients), allogeneic one HLA-haplotype-identical (3 patients), syngeneic (3 patients), or autologous (1 patient) marrow grafting. E rosette-positive (T) and E rosette-negative (non-T) peripheral blood mononuclear cells were cocultured with pokeweed mitogen for 6 days. Polyvalent immunoglobulin secretion was determined by counting plaque forming cells in a reverse hemolytic plaque assay. The number of antibody secreting cells in cocultures of autologous T and non-T lymphocytes was low in 40 of 44 tests conducted on samples from the 37 patients. Mononuclear or non-T cells from 38 of 40 tests failed to produce antibody when cultured with normal helper T cells. T cells from 23 of 37 tests failed to help normal non-T cells secrete antibody. T lymphocytes from 23 of 41 tests suppressed antibody production greater than 80% by normal T and non-T cells. The suppressor cells were radiosensitive in 17 of the 25 tests. The abnormal function of lymphocyte subpopulations in patients during the first 3 mo after syngeneic, allogeneic or autologous marrow grafting was similar regardless of the type of graft or the presence of acute graft vs host disease. (Author abstract) (29 Refs)

12. LEUKEMIA: HISTORICAL DEVELOPMENT OF CANCER THERAPY: THE FIRST BATTLE IS WON.

Evans AE
Div. Oncology, Cancer Center, Children's Hosp. Philadelphia, Univ. Pennsylvania, Philadelphia, PA, 19104
Front Radiat Ther Oncol; 16:18-29 1982

The combination chemotherapy protocols which had been developed by 1975 increased the 5-yr disease-free survival (DFS) rate to 50% in children with acute lymphocytic leukemia (ALL). Most relapses occur in the first 2.5 yr. When maintenance therapy is given for 5-6 yr instead of 2.5-3 yr, the DFS rate is not greatly increased, except in boys who tend to develop testicular involvement. Studies on the natural history of childhood ALL have led to the formulation of a set of prognostic factors: age (the best prognosis is in children 2-10 yr old), sex (the prognosis is better in girls than in boys), initial WBC count, the presence or absence of CNS involvement and/or a lymphoma syndrome (elevated Hb, markedly enlarged liver, spleen, and lymph nodes, and/or a mediastinal mass), IgG levels (depression of IgG is an unfavorable sign), FAB markers on the leukemic blasts, and marrow status on day 14 of therapy. The presence of B- or T-cell markers on the leukemic cells is not in itself a major factor. The unfavorable prognosis of T-cell ALL is primarily related to its association with older age, male sex, a high WBC count, and a mediastinal mass. If these factors are not present, the occurrence of T-cell markers is not an unfavorable factor in itself. The 5-yr DFS rate in children having a good prognosis is now 90%. It may be possible to achieve equally good results in these patients with less intensive therapy. Recent advances in treatment have not given such good results in acute leukemias other than ALL. High-dose chemotherapy and total-body radiation, followed by bone marrow transplants from an HLA-identical sibling, have led to a 2-yr survival rate of 60%, if this treatment is given during the first remission. The late effects of successful treatment are now being investigated. (30 Refs)

13. 'TARGET' CELLS, CELLULAR PHENOTYPES, AND LINEAGE FIDELITY IN HUMAN LEUKAEMIA.

Greaves MF
Membrane Immunology Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
J Cell Physiol; Suppl1:113-125 1982

Features of leukemic phenotypes in relation to normal hemopoietic differentiation were investigated in a study developed as a part of a routine immunodiagnostic service for leukemia in the United Kingdom (UK). Leukemic samples (heparinized blood, lymph node biopsies, cerebrospinal fluid, and peritoneal aspirates) were obtained from referring hospitals throughout the UK. A presumptive normal sequence of antigen (and other marker) expression in T cell differentiation is presented. The scheme is based upon reported antigenic heterogeneity of cortical and medullary thymocytes and subsets of blood T cells. The corresponding maturation 'positions' of 95 leukemic T cell phenotypes analyzed are presented. T-acute lymphoblastic leukemia (T-ALL), and T-non-Hodgkin's lymphoma in childhood 'correspond' to early or late thymocyte populations while T cell leukemias or lymphomas of older (greater than 35 yr) patients diagnosed as cutaneous lymphoma or leukemia, chronic lymphocytic leukemia, prolymphoblastic leukemia, or lymphoblastic lymphoma, all had 'mature' T phenotypes. The phenotypes that were documented in non-T-ALL are summarized. The majority of complementary ALL that do not synthesize detectable mu chain nevertheless have rearranged mu chain genes as revealed by molecular hybridization studies. Alterations in phenotype during leukemia progression or relapse may provide some evidence for distortion of 'normal' genetic programs as well as revealing the lineage affiliations of various clonogenic populations. Alterations in the latter population may indirectly indicate the possible target cell population involved. (89 Refs)

14. IN SITU - DEMONSTRATION OF HELPER-T-LYMPHOCYTES IN CUTANEOUS MALIGNANT LYMPHOMAS BY DIAMINOPEPTIDASE IV (DAP IV).

Sterry W, Steigleder GK, Goos M, Meisterernst E
Universitat-Hautklinik, Joseph-Stelzmann-Strasse 5, D-5000 Koln 41, W. Germany
Z Hautkr; 57(8):567-570,573-576 1982

Sections of frozen material from lesions of patients without treatment were used for enzymes diaminopeptidase IV (DAP

IV), unspecific acid esterase, and beta-glucuronidase determination. Helper-T-lymphocytes were demonstrated in tissue sections of cutaneous lymphoma by the DAP IV; the majority of DAP IV positive cells was found in plaque stage of mycosis fungoides, but DAP IV positive cells decreased considerably in malignant lymphomas. The DAP IV can be used for demonstration of normal and neoplastic helper-T-lymphocytes. (16 Refs) (In GER)

15. MORPHOLOGIC OBSERVATIONS OF CONTACT-INDUCED LYSIS OF EBV-INFECTED B LYMPHOCYTES BY AUTOLOGOUS HAND MIRROR T CELLS.

Thomas WJ, Duval-Arnould B, Creegan WJ, Schumacher HR, Forman DS, Strong DM
Clinical Investigation Center, Naval Regional Medical Center, San Diego, CA, 92134
Am J Hematol; 12(2):109-119 1982

To study the possible immunologic role of hand mirror lymphocytes (HML) in the control of Epstein-Barr virus (EBV)-infected B lymphocytes in patients with infectious mononucleosis (IM), we studied the in vitro interactions of these cells by time-lapse video light microscopy. Peripheral blood T lymphocytes isolated from three patients in the early recovery phase of IM were mixed with their autologous EBV-infected B cells. Motile lymphocytes with their characteristic hand mirror shape were observed to attach by their uropods to the B cells. The HML remained attached for variable periods ranging from 45-75 min. Following detachment, B cells that were in contact with HML underwent lysis. Mixtures of T cells from healthy donors and EBV-infected cell lines exhibited only rare uropod formation with no attachment or lysis of B cells. The present experiment indicates that contact-induced lysis of EBV-infected B lymphocytes is operative in IM and that this process is mediated by the HML. (Author abstract) (31 Refs)

16. SERA FROM PATIENTS WITH UNDIFFERENTIATED NASOPHARYNGEAL CARCINOMA CONTAIN A FACTOR WHICH ABROGATES SPECIFIC EPSTEIN-BARR VIRUS ANTIGEN-INDUCED LYMPHOCYTE RESPONSE.

Sundar SK, Ablashi DV, Kamaraju LS, Levine PH, Faggioni A, Armstrong GR, Pearson GR, Krueger GR, Hewetson JF, Bertram G, Sesterhenn K, Menezes J
(c/o Menezes) Lab. Immunovirology, Pediatric Res. Center, St. Justine Hosp., 3175 Cote St. Catherine, Montreal (Quebec) H3T 1C5, Canada
Int J Cancer; 29(4):407-412 1982

A unique association of Epstein-Barr virus (EBV) with the undifferentiated nasopharyngeal carcinoma (NPC) is a well acknowledged phenomenon. We report here the detection of a factor present in the sera of NPC patients which inhibits the blastogenic response of lymphocytes from EBV seropositive individuals to EB virions or soluble antigens. This lymphocyte-stimulation inhibitor (LSI) was found to be associated with the IgA fraction of the serum immunoglobulins. No inhibitory activity was detected in the sera and their immunoglobulin fractions from healthy (both EBV-seropositive and seronegative) individuals and patients with other carcinomas of the head and neck region. Interestingly, the IgA-LSI was absent in the sera of NPC patients who were successfully treated and remained in remission, while it was readily detectable in the sera of NPC patients in relapse. LSI-positive IgA fractions did not inhibit mitogenic response of lymphocytes to phytohemagglutinin. Taken together, the data presented suggest that LSI is a specific inhibitor of the response of sensitized lymphocytes to EBV antigens and that it may indeed represent a marker of great clinical significance regarding undifferentiated nasopharyngeal carcinoma, particularly for its prognosis. (Author abstract) (36 Refs)

17. DOES ENDOGENOUS CORTISOL PLAY A ROLE IN THE DEVELOPMENT OF CANCER?

Klein A
Endocrinological Lab., Beilinson Medical Center, Petah-Tiqva 49100, Israel
Med Hypotheses; 8(2):163-171 1982

Studies have shown an inverse relationship between physiological levels of cortisol and the number of lymphocytes in circulation, and the importance of lymphocytes ability to metabolize cortisol in the process of regulating the lymphocyte population. A blood factor called lymphocytic-cortisol-metabolism-enhancing factor (LCMEF) serves to maintain the homeostatic balance by enhancing cortisol metabolism by lymphocytes, thus acting as a counter-agent against the cortisol effects. The lack of LCMEF, preceding the development of malignancy, can induce lymphopenia, seen in cancer patients, and the depletion of cortisol-sensitive lymphocytes involved in the immune response against malignant cells. The cortisol effect would also explain the development of cancer in transplant patients who have undergone immunosuppression therapy. (43 Refs)

18. PLASMAPHERESIS IN PATIENTS WITH ADVANCED MALIGNANT DISEASE: A PILOT STUDY.

Micksche M, Colot M, Kokoschka EM, Moser K, Rainer H
Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Vienna, Austria
Oncology; 39(3):146-151 1982

Plasmapheresis has been performed in 16 patients with advanced malignant disease (12 malignant melanoma, 2 breast cancer, 2 colon cancer). Up to 3,000 ml of plasma (range 1,650-3,000 ml) have been replaced by one single plasma exchange. Side effects observed in about 50% of the patients were mainly nausea and chills. Serum proteins including acute phase reactants were monitored before and 2, 4, and 7 days after plasma exchange. A transient change of these proteins was observed in the first days, but, later on, pretreatment values were always regained. Peripheral blood lymphocyte blastogenic response to mitogens was increased in five out of nine patients 7 days after plasma exchange. In seven out of nine patients pretreatment serum was found inhibitory to autologous lymphocyte reactivity to mitogens. Furthermore, plasmapheresis was found to decrease significantly the blocking effect of patients' sera on normal donor lymphocyte reactivity. Plasmapheresis was found tolerable in all patients treated, but without any clinical efficacy. Further studies are warranted to establish the therapeutic value of plasma exchange in patients with advanced malignancies. (Author abstract) (19 Refs)

19. LYMPHOCYTE TRANSFORMATION INDUCED BY AUTOLOGOUS CELLS. XII. QUANTITATIVE AND QUALITATIVE DIFFERENCES BETWEEN HUMAN AUTOLOGOUS AND ALLOGENEIC REACTIVE T LYMPHOCYTES.

Kozak RW, Moody CE, Staiano-Coico L, Weksler ME
Dept. Medicine, Cornell Univ. Medical Coll., New York, NY, 10021
J Immunol; 128(4):1723-1727 1982

The T cell populations that respond to autologous or allogeneic non-T cells are distinct, at least to a considerable extent. This conclusion is based on the differences in (a) the size of the two populations; on the average 1 in 260 (individual frequency range, 1:149 to 1:417) T cells respond to allogeneic non-T cells whereas 1 in 3,100 (individual frequency range, 1:2,200 to 1:5,000) T cells respond to autologous non-T cells; (b) the phenotype of T cells activated in the MLR; autoactivated T cells were drawn predominantly from the OKT4-reactive T cell subpopulation, whereas alloactivated T cells activated in the allogeneic MLR were drawn from the OKT4, OKT5, and OKT8-reactive T cell subpopulations; and (c) the specificity of activated and nonactivated T cells obtained on Percoll gradients after autologous or allogeneic MLR. Auto- or allodepleted T cells recovered from the 55 to 60% Percoll interface retained full alloreactivity or autoreactivity, respectively. However, auto- or alloactivated T cells recovered from the 40 to 50% Percoll interface showed secondary kinetics to allogeneic and autologous non-T cells. Whether the alloreactivity or autoreactivity found in autoactivated or alloactivated T cells, respectively, represents true cross-reacting T cells or T cells nonspecifically recruited during the MLR cannot at present be decided. (Author abstract) (19 Refs)

20. BLOOD T-LYMPHOCYTE FUNCTIONS IN HEALTHY ADULTS IN RELATION TO AGE.

Wedelin C, Bjorkholm M, Holm G, Ogenstad S, Mellstedt H
Dept. Medicine, Div. Hematology, Danderyd's Hosp., S-182 88 Danderyd, Sweden
Scand J Haematol; 28(1):45-53 1982

Blood T-Lymphocyte functions were studied in 167 healthy adults (age range 19-91 years). Lymphocyte DNA synthesis induced by concanavalin A, pokeweed mitogen and PPD antigen declined with age while the spontaneous DNA synthesis remained essentially unchanged. Relative and total T-cell counts but not total lymphocyte counts were moderately decreased in elderly persons. The lymphocyte response to mitogens correlated with the PPD-induced activation in vitro. Lymphocyte and T-cell counts did not show any association with the response to mitogens and antigen. A few subjects were tested on several occasions during 2-7 yr confirming a good reproducibility of the techniques employed. Thus aging is associated with diminished number of T-cells and impairment of lymphocyte activation by T-cell mitogens and PPD antigen. The clinical importance of this general age-related T-cell deficiency remains largely unresolved. (Author abstract) (30 Refs)

21. EFFECT OF SYSTEMIC INTERFERON ON NATURAL KILLER CELL FUNCTION IN MELANOMA PATIENTS.

Golub SH, Burk M
Univ. California Los Angeles, Los Angeles, CA
UCLA Cancer Cent Bull; 9(1):3-6 1982

The effect of human leukocyte interferon on natural killer (NK) cell function was examined in patients with disseminated malignant melanoma. Treatment of 16 patients with human leukocyte interferon was not associated with any notable change in the proportion or absolute number of major lymphocyte subpopulations, including T and B cells and Fc receptor cells. When NK activity was tested against the myeloid leukemia target K562, NK activity declined at 24 hr after the first administration of interferon. Subsequently, activity rose, with peak activity found at 7 days of continuous daily treatment. When five patients who may have had some clinical benefit from interferon treatment were compared with four patients with rapid disease progression, no difference in the degree to which NK cytotoxicity was augmented by interferon was seen. Results of cellular analysis suggested that in vivo treatment with interferon results in both an increase in cytotoxicity by mature NK cells and recruitment of additional cells from precursors of NK cells into the NK differentiation pathway. (7 Refs)

22. CELLULAR IMMUNITY IN CARCINOMA OF CERVIX.

Pasqualini RS, Giraudo Conesa LC, Chevallier R
Departamento de Medicina Nuclear e Investigacion Inmunologica,, Instituto de Investigaciones Hematologicas Academia Nacional de Medicina, Buenos Aires, Argentina
Medicina (B Aires); 41(Suppl):155-160 1981

Cellular immunity was determined by means of inhibition of leukocytic migration (IML) in 27 patients (22-77 yr old) with invasive squamous cell carcinoma of the cervix before any treatment, and in 18 healthy controls (HC). According to clinical classification, 7 of the patients were in Stage I, 7 were in Stage II, 12 were in Stage III, and 1 in Stage IV. Effect of levamisole, peptichemio, and phytohemagglutinin on IML was studied in some of the patients. Effect of cell free extract of the carcinoma on the migration of leukocytes in vitro, if possible on the liberation of the inhibition factor from lymphocytes, and of the migration and inhibition factor from leukocytes, was determined in all the patients. IML was observed only in 36% of the patients with autologous tumoral extract, and in 18% with homologous tumoral extract. Number of patients, who showed reactivity to IML decreased with more advanced clinical stages, more immature histologic type, and with bad evolution of the disease. Changes in immunocompetence occur already in early stages of the disease, although it is not clear at this point, if they precede appearance and/or evolution of the disease or are its consequence. (18 Refs) (In SPA)

23. UNUSUAL FEATURES OF INFECTIONS IN THE AGING.

Finkelstein MS
New York Univ. Medical Center, 550 First Ave., New York, NY, 10016
Geriatrics; 37(4):65-67,71,73-75,78 1982

Infectious disease problems of the elderly are discussed, including those related to humoral changes; changes in cell-mediated immunity; macrophages, polymorphonuclear neutrophilic leukocytes, eosinophils; causes of immune senescence; complement systems, fever, sedimentation rate; nonimmunologic factors; specific infections; and treatment. Recovery in the older patient lies more in immunologic defenses than in drug or surgical intervention. Decreased immunosurveillance against tumor development in the sixth decade is correlated with an increased incidence of malignancy. (26 Refs)

24. PURE RED CELL APLASIA AND CHRONIC LYMPHOID LEUKEMIA. THE USEFULNESS OF FERROKINETIC MEASUREMENTS.

Viala JJ, Ville D, Coiffier B, Rebattu P, Guastalla J
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Nouv Rev Fr Hematol; 23(4):213-218 1981

Three cases of RBC aplasia during chronic lymphocytic leukemia (CLL) are reported. Patients included a woman (60-yr-old) and two men (39 and 62 yr old). In all cases the anemia appeared suddenly with the patient experiencing extreme fatigue. Splenomegaly was present in two patients. Ferrokinetic measurements were helpful in the diagnosis of the nonhemolytic anemias. Total erythropoietic insufficiency with an absence of reticulocytes and absence of RBC utilization of radioactive iron were observed. Cortisone therapy was successful in controlling the first episodes of anemia. In two cases there were relapses which were controlled through splenectomy and further cortisone therapy. One patient died 3 yr later without recurrence of anemia. The patient who underwent splenectomy was free of anemia 18 mo following treatment despite continuation of chemotherapy. The third patient was free of anemia at 9 mo follow-up. Although RBC anemia during CLL is rarely observed, the onset is sudden and can lead to rapid patient deterioration unless promptly treated with cortisone or immunosuppressive therapy. (17 Refs) (In FRE)

25. EFFECT OF L-PHENYLALANINE MUSTARD, ADRIAMYCIN, ACTINOMYCIN D, AND 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDIDE ON NATURALLY OCCURRING HUMAN SPONTANEOUS MONOCYTE-MEDIATED CYTOTOXICITY.

Kleinerman ES, Zwelling LA, Schwartz R, Muchmore AV
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Cancer Res; 42(5):1692-1695 1982

We have shown previously that cis-diamminedichloroplatinum(II) (cis-DDP), an active antineoplastic agent, and x-irradiation enhanced human spontaneous monocyte-mediated cytotoxicity in vitro. To ascertain whether this is a unique property of cis-DDP or common to other effective antineoplastic agents, we studied the effect of L-phenylalanine mustard (L-PAM), Adriamycin (ADR), actinomycin D, and 4'-(9-acridinylamino)methanesulfon-m-anisidide (m-AMSA) on spontaneous monocyte-mediated cytotoxicity. cis-DDP, ADR, L-PAM, and m-AMSA under appropriate in vitro conditions all increased spontaneous monocyte-mediated cytotoxicity. Activation involved (a) direct monocyte activation (cis-DDP and ADR); (b) inactivation of suppressor lymphocytes (x-irradiation); (c) a combination of the two (L-PAM); or (d) mechanisms not yet elucidated (m-AMSA). In contrast, incubating mononuclear leukocytes with 0.4 ug actinomycin D per ml depressed monocyte-mediated killing . Thus, while stimulation of 'nonspecific' killing is not a unique property of cis-DDP, it is not a universal effect of all chemotherapeutic agents. The stimulation and enhancement of already existing host defense mechanisms may be an important additional way in which many chemotherapeutic agents exert their antitumor effect. (Author abstract) (27 Refs)

26. DEFICIENT NATURAL KILLER CELL ACTIVITY IN A PATIENT WITH FANCONI'S ANAEMIA AND SQUAMOUS CELL CARCINOMA. ASSOCIATION WITH DEFECT IN INTERFERON RELEASE.

Hersey P, Edwards A, Lewis R, Kemp A, McInnes J
Medical Res. Dept., Kanematsu Memorial Inst., Sydney Hosp., Sydney, N.S.W. 2000, Australia
Clin Exp Immunol; 48(1):205-212 1982

A child with Fanconi's anemia diagnosed at 7 yr of age presented in adult life with lymphopenia, recurrent warts and Bowen's disease. The latter resulted in the development of multiple cutaneous squamous cell carcinomas which metastasized to the skeleton. Investigation of her immune function revealed selective defects in natural killer (NK) cell activity. Humoral immunity and several tests of cell-mediated responses were within normal or became normal after treatment with levamisole or transfer factor. Analysis of the defect in NK activity revealed that low levels could be induced in vitro by fibroblast interferon. Stimulation of blood lymphocytes from the patient with the interferon inducer poly(I)-poly(C) resulted in an increase in NK activity but incubation of her lymphocytes on tumor cells did not result in an increase in NK activity or the release of interferon. This contrasted with the marked increase in NK activity and interferon release observed when lymphocytes from normal controls were incubated on tumor cells. These findings suggested the absence of NK activity in this patient was secondary to a defect in interferon release from lymphocytes on exposure to tumor antigens. It is considered that these defects may have been an important predisposing factor in the development of malignancy in this patient and possibly other patients with Fanconi's anemia. (Author abstract) (20 Refs)

27. NATURAL KILLER ACTIVITY IN SPLEENS AND LYMPH NODES FROM PATIENTS WITH HODGKIN'S DISEASE.

Ruco LP, Procopio A, Uccini S, Marcorelli E, Baroni CD
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Cancer Res; 42(5):2063-2068 1982

Natural killer (NK) activity against K-562 myeloid cell line was evaluated in 21 spleens and 14 lymph nodes from patients with Hodgkin's disease (HD). NK activity of eight HD-involved (HD-) spleens [556 lytic units (LU)] was found five-fold higher than that of 13 HD-uninvolved (HD-) spleens (112 LU) (p less than 0.01). Moreover, NK activity of HD+ spleens was significantly different (p less than 0.05) from that of three spleens involved by non-HD lymphoma (100 LU). NK activity of four spleens from nonneoplastic patients (250 LU) was intermediate between those of HD+ and HD- spleens. Lymph node cells were about 10-fold less cytotoxic. NK activity of seven HD+ lymph nodes (43 LU) was three-fold higher than that of three lymph nodes involved by non-HD lymphoma (8 LU). However, these differences were not statistically significant. Our data are compatible with increased NK activity in HD+ tissues as well as with depressed NK activity in HD- tissues. The observation that NK activity of peripheral blood leukocytes from nine HD patients (116 LU) (p less than 0.05 only at 100:1 effector:target cell ratio) may support the latter interpretation. Partial characterization of effector cells in HD+ and in HD- spleens indicated that, in both instances, NK cells were nonadherent and almost equally distributed between the erythrocyte-negative and -positive cell fractions. Finally, NK activity of both HD+ and HD-spleen cells could be further potentiated in vitro by interferon. (Author abstract) (30 Refs)

28. NATURAL KILLER CELL ACTIVITY IN GASTROINTESTINAL CANCER PATIENTS - DECLINE IN NATURAL KILLER CELL ACTIVITY IN TGAMMA CELLS AND THE ACTION OF INTERFERON ON ITS INCREASE.

Mugitani H, Suzuki M, Naruki Y, Ohtsuka S, Shinbo T
First Dept. Internal Medicine, Toho Univ. Sch. Medicine, Ota-ku, Tokyo, Japan
Nippon Gan Chiryo Gakkai Shi; 16(7):1371-1376 1981

Effects of interferon (IF) on natural killer (NK) cell activity of Tgamma-cells (IgG-Fc receptor-positive T cells) were investigated in peripheral blood lymphocytes of 21 patients with gastrointestinal cancer (17 gastric, 2 esophageal, 1 large intestine, and 1 gall bladder). T cells were isolated from peripheral blood lymphocytes, using the E-rosette sedimentation reaction; Tgamma-cells were isolated using theophylline. Release of 51Cr from 51Cr-labeled K562 cells was used to measure the NK cell activity. In 10 healthy subjects, the NK cell activity of mononucleocytes (MNC) was 46.5 +-13.1% and that of

Tgamma-rich cells was 47.7 +-11.3%; these values were used as standards for NK cell activity in determinations of cytotoxic index. The cytotoxic index was applied to the NK cell activities of lymphocytes of the patients. The Tgamma cells showed a decline in NK cell activity in most of the 21 patients; there was also a decrease in NK cell activity in the MNC in these patients. Addition of 1,000 units of IF increased the NK cell activity of the MNC, T-rich and Tgamma-rich cells. The results suggested that the decreased NK cell activities of the Tgamma cells and the MNC may be due to decreased effector cell functioning and decreased production of IF. (27 Refs) (In JPN)

29. NATURAL CYTOTOXICITY AND ANTIBODY-DEPENDENT CYTOTOXICITY IN SOLID TUMOR CANCER PATIENTS: REGULATION BY ADHERENT CELLS.

DeBoer KP, Braun DP, Harris JE
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Clin Immunol Immunopathol; 23(1):133-144 1982

Natural cytotoxicity (NK) and antibody-dependent cellular cytotoxicity (ADCC) were measured in peripheral blood mononuclear cells (PBMC) from 30 normal subjects and from 60 untreated patients with solid tumors at various stages of disease. NK, but not ADCC, activity of PBMC from patients with disseminated disease was significantly lower than NK activity of either normal donors or patients with localized disease. This decreased NK activity was not related to decreased numbers of T cells or target-binding cells or to immune complex levels in patient sera. Glass-adherent cell depletion augmented decreased NK levels significantly to normal levels of function. Addition of indomethacin did not alter NK activity in any of the patients studied. We conclude that decreased NK activity in PBMC from cancer patients with disseminated disease is due to a suppression which may be mediated by glass-adherent cells. This is not dependent on a prostaglandin-mediated mechanism of suppression. (Author abstract) (28 Refs)

30. IMMUNOLOGIC STUDIES ON CANCER OF THE UPPER AERODIGESTIVE TRACT.

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Dept. Otorhinolaryngology, Mayo Clinic and Mayo Foundation, Rochester, MN
Otolaryngol Head Neck Surg; 90(1):52-57 1982

A series of cold target natural killer (NK) inhibition assays against the K562 cell line were performed. NK susceptibility of Epstein-Barr virus (EBV)-related cell lines increased with increasing viral expression within the cells. Thus, infection with and induction of the EBV genome may result in increased susceptibility to NK lysis. Preliminary studies of patients with head and neck cancer revealed two distinct clusters of either high or low reactivity. (14 Refs)

31. REDUCED NATURAL KILLER CELL ACTIVITY IN NON-HODGKIN'S LYMPHOMA.

Neri A, Brugiatelli M, Ozger Topuz U, Astaldi G
(c/o Astaldi) Centre Emetololgico, Istituto 'Citta di Pavia', Viale Parco Vecchio, 27, 27100 Pavia, Italy
Boll Ist Sieroter Milan; 60(5):394-407 1981

A literature review is followed by a study of the natural killer (NK) activity in 20 patients with non-Hodgkin's lymphoma (NHL) and in 20 age-matched healthy subjects. The NHL patients included 3 with nodular, and 17 with diffuse histology, aged 24-69 yr. All but three were under treatment with multiple chemotherapeutic agents; however, at time of study none had received therapy during the previous 4 wk. Effector cells were lymphocytes separated from cubital vein blood; cells of the K 562 myeloid cell line were used as target cells. Experiments were carried out at effector/target ratios of 20:1 or 40:1 in the 4-hr Cr release assay. Compared with controls, the NHL patients showed reduced NK activity. However, a statistically significant reduction was found only in the group of patients with active disease, either at onset or at relapse. Patients in clinical remission displayed a more moderate decrease of NK cell activity. It is suggested that the study of NK function might be a helpful tool in following the clinical course and efficacy of treatment in NHL. (126 Refs)

32. INFECTIONS AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Iwarson S
Infektionskliniken, Ostra sjukhuset, Goteborg, Sweden
Lakartidningen; 79(13):1225 1982

The recent considerable increase in the incidences of opportunistic infections and Kaposi's sarcomas among homosexual men in the United States of America and their possible causes are discussed. The factor common to both phenomena is a general immunosuppression which may be due to cytomegalovirus infection or reactivation, to the abuse of certain drugs, and the combination of infection and drug abuse. (5 Refs) (In SWE)

33. DISEASES ASSOCIATED WITH IMMUNOSUPPRESSION.

Heise ER
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Environ Health Perspect; 43:9-19 1982

Impairment of any of the major components of the immune system (T-cells, B-cells, phagocytes, complement) may result in clinical immunodeficiency. Immune defects can arise from intrinsic or heritable defects of lymphoid elements, failure of normal cellular differentiation, viral infection or other acquired causes. Clinical impairment of immunity is expressed as a marked susceptibility to opportunistic and pathogenic organisms which are difficult to control and by an increased risk of malignancy, allergy and autoimmune disease. Certain immunodeficiency disorders are associated with aberrant immune regulation. The major types of immune deficiency are characterized by unique patterns of infections depending on the level at which the defect occurs and the pathogenic mechanisms of the parasite. The basic defects of representative primary and secondary immunodeficiencies are discussed in relation to observed immunologic consequences. (Author abstract) (51 Refs)

34. HUMAN PAPILLOMAVIRUS AND ONCOGENESIS.

Jablonska S
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Z Hautkr; 57(8):551-552,555-560,563,566 1982

Human papillomaviruses (PV) and oncogenesis were discussed, and the following aspects were included oncogenic properties of animal PV, carcinomas and human PV (PV of larynx in children, genital warts, cervical dysplasia, Bowen's disease, epidermodysplasia verruciformis (EV), the EV induced by human PV-3 and PV-5, cellular immunity (CI), specific CI, and specific humoral immunity), and genetics (importance of determination of types of human PV). (72 Refs) (In GER)

35. SOME IMMUNOLOGICAL STUDIES OF ESOPHAGEAL CANCER IN MAN.

Hui ZY
Cancer Inst., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

General immunocompetence and the specific immune response against esophageal cancer (EC) were studied in EC patients. The ability of lymphocytes to transform in vitro in the presence of mitogen and the ability of macrophages to phagocytose foreign particles appear to be impaired in EC patients. EC probably has tumor-associated antigen which is immunogenic: the putative EC-associated antigen can induce specific immune responses in the host which are both cell-mediated and humoral. Data on phagocytic activity of human macrophages and phagocytic activity in 35 cancer patients are presented. (no Refs)

36. MODULATION OF THE IMMUNE SYSTEM - A NEW PRINCIPLE IN THE TREATMENT OF CHRONIC DISEASES.

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Tech Mitt; 74(11/12):609-612 1981

Potential use of immunomodulators in the treatment of patients with chronic diseases (including cancer) that affect the immune system is discussed. The function, development, and interaction of various types of cells within the immune system are described. The fact that diseases affecting the immune system occur more frequently in older people is noted. The history of attempts to modulate the immune system is outlined; among the substances discussed are BCG, Corynebacterium parvum, levamisole, thymosin, and interferon. The role of the immune system in the development of cancer is examined with regard to cellular defenses against malignant cells, information gained from the study of athymic mice, and the fact that the cytostatics used in cancer chemotherapy are often immunosuppressors. Studies of the effects of immunomodulators in tumor-bearing are described. The immunomodulators used were 2-cyanaziridine derivatives. Two of these immunomodulators that were tested prevented the growth of pulmonary metastases in mice bearing Lewis lung tumors,; no effect on the primary tumors was observed. In addition, these same immunomodulators reduced the incidence of infection in mice injected with fungi after exposure to a chemotherapeutic (immunosuppressive) agent. The effect of these immunomodulators in animals with autoaggression diseases is described also. (no Refs) (In GER)

37. EFFECT OF SERA OF CANCER PATIENTS ON ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC).

Fekete B, Forrai I, Garam T, Angyal I, Pal A, Bakacs T
Orszagos Koranyi Tbc es Pulmonologiai Intezet, Budapest, Hungary
Magy Onkol; 26(1):13-18 1982

The ADCC-inhibiting effects of serum samples from 38 patients (24 men and 14 women, av age 58.7 yr) with inoperable lung cancer, 49 patients (37 men and 12 women, av age 56.2 yr) with operable lung cancer, 41 women (av age 35.7 yr) with operable breast cancer, and 28 patients (24 men and 4 women, av age 56.5 yr) with chronic bronchitis were studied to assess the value of the ADCC inhibition test in the diagnosis of cancer. Healthy blood donors (41 men and 16 women, av age 37.7 yr) served as controls. The av ADCC inhibition rates were 33.3-49% in the controls, 55.9% in the operable lung cancer patients, 66.2-79.2% in the inoperable lung cancer patients, and 42.8-54.5% in the patients with chronic bronchitis. The differences were significant between the operable and inoperable lung cancer patients, as well as between the lung cancer patients as a whole and the controls and patients with chronic bronchitis. The cancer patients and controls were discriminated from one another at an accuracy of 85-100% by the ADCC inhibition test. The corresponding percentages of correct discrimination were 55-65% between the donors and the patients with chronic bronchitis and 76-100% between the patients with chronic bronchitis and the cancer patients. (37 Refs) (In HUN)

38. CELL-MEDIATED IMMUNITY AND ITS APPLICATION IN TOXICOLOGY.

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Environ Health Perspect; 43:31-36 1982

A variety of in vivo and more recently in vitro assays have been described to assess cell mediated immunity (CMI). Two methods routinely employed in our laboratory to assess CMI following exposure to chemicals in rodents included delayed hypersensitivity and in vitro lymphoproliferation. Preliminary studies indicate that depressed delayed hypersensitivity responses, as performed by a radiometric assay, correlates with altered susceptibility to infectious agents and tumor cell challenge following exposure to immunotoxic chemicals. Furthermore, suppression of T-cell lymphoproliferative responses to at least 50% below control values correlated with depressed delayed hypersensitivity responses and altered host susceptibility. On the other hand, when suppression of T-cell lymphoproliferative responses are within 50% of control values, delayed hypersensitivity and host susceptibility parameters are not affected. Assuming adequate technical expertise and accurate data interpretation. CMI assays of these types can provide a valuable data base for toxicology studies and immunotoxicity assessment. (Author abstract) (21 Refs)

39. CHEMOTHERAPY-INDUCED IMMUNOSUPPRESSION.

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Environ Health Perspect; 43:21-25 1982

Chemotherapeutic agents are used widely in clinical medicine for the treatment of conditions where diminution of the host immune response is a goal. The clinical use of immunosuppression is indicated for immunologically mediated disease, lymphoproliferative diseases, and prevention of graft rejection. Five categories of agents are useful for these purposes; they are ionizing irradiation, corticosteroids, biological alkylating agents, antilymphocyte sera and antimetabolites. While the specific molecular action of many of these drugs is known, how they affect cellular events in immune responses is less clear. One of the unfortunate sequelae of chemotherapy induced immunosuppression is an increased susceptibility of the host to opportunistic pathogens or malignancies. Specific methods are described for monitoring the various parameters of both humoral and cellular immunity. Studies of immunologic function in lymphoma patients and cardiac transplant patients treated with immunosuppressive drugs have shown specific defects in cell mediated immunity to herpes viruses which may relate to their increased susceptibility to infection by these agents. (Author abstract) (9 Refs)

40. EULAR REGISTER OF PATIENTS ON IMMUNOSUPPRESSIVE DRUGS.

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ARC Epidemiology Res. Unit (Clinical Section), Dept. Rheumatology, Guy's Hosp., London SE1, England
Ann Rheum Dis; 41(Suppl1):30-31 1982

In 1979, the European League Against Rheumatism (EULAR) began a follow-up study of patients receiving immunosuppressive therapy for rheumatoid arthritis and related diseases. The group now includes 716 patients (av age 55 yr); 478/716 began immunosuppressive therapy during 1979 or 1980 and 238/716 began therapy before 1979. Patient registration continues. The agents most often taken are azathioprine (APR: 447/716) and cyclophosphamide (CP: 155/716). The malignancy rate cannot yet be estimated, but one patient taking CP and six patients taking APR have developed malignancies. The first full analysis of the findings will be undertaken in 1983. (no Refs)

41. IMMUNOLOGIC EVALUATION OF PATIENTS WITH POLYCHLORINATED BIPHENYL POISONING: EVALUATION OF DELAYED-TYPE SKIN HYPERSENSITIVE RESPONSE AND ITS RELATION TO CLINICAL STUDIES.

Chang KJ, Hsieh KH, Tang SY, Tung TC
Coll. Medicine, Natl. Taiwan Univ., Taipei, Taiwan, Republic of China
J Toxicol Environ Health; 9(2):217-223 1982

Association of suppressed cellular immune function with other polychlorinated biphenyl (PCB) poisoning symptoms was investigated. Results of the delayed-type skin hypersensitive response to streptokinase and streptodornase showed a positive response in 80% of normal human subjects compared to 43% of PCB poisoned patients. Suppression of cellular immunity was positively correlated with PCB lesion severity. Size of induration was negatively correlated with whole blood PCB concentrations and positively correlated with the percentage of active T cells. The suppression of delayed-type skin hypersensitive response is associated with a decreased percentage of T cells forming active T cell rosettes. (13 Refs)

42. DIPHTHERIA TOXIN TREATMENT OF HUMAN ADVANCED CANCER.

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Cancer Res; 42(5):2054-2058 1982

Purified diphtheria toxin was administered iv to 50 patients with advanced solid tumors. The doses of toxin varied according to the different immunological status of the patients against diphtheria. The prominent toxic effects of the treatment were transient peripheral neuropathy observed in two nonimmune patients and fever (37-41 C) which occurred in all immune patients with cell-mediated hypersensitivity to toxin. A partial response lasting from 2-4 wk was achieved in 3 of 13 nonimmune patients and in 1 of 3 nonimmune patients with cell-mediated hypersensitivity. Of 21 immune patients, 9 had partial response lasting from 4-12 wk. Of 13 immune patients with cell-mediated hypersensitivity, six had partial and five complete response lasting from 2-12 and from 1-25+ mo, respectively. The overall response rate was 48%. The results suggest that diphtheria toxin may have a role in cancer immunotherapy. (Author abstract) (15 Refs)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

43. INFLUENCE OF SELECTIVE ABSENCE OF H-2KKAPPA ON GROSS VIRUS LEUKAEMIAS IN VITRO AND THE IMPLICATIONS FOR IN VIVO SURVEILLANCE OF LEUKAEMIA.

Festenstein H, Schmidt W, Alonzo A, Leben L
Dept. Immunology, London Hosp. Medical Coll., London, England
Protides Biol Fluid Proc Colloq; 29:231-235 1982

Results are presented of direct complement dependent cytotoxicity tests using anti H-2Kkappa (H-2Kk) monoclonal antibody on five primary AKR leukemias. These and earlier results permit the conclusion that the absence/reduction of the H-Kk gene product is not uncommon in Gross virus leukemia. In search of the biological implication of this finding, a comparison was made of the ability of the K-GV BALB/c Gross virus tumor, which lacks Kk, and other Gross virus tumors with normal H-2Kk representation, to act as targets in cell mediated lympholysis (CML). Results showed that resistance to syngeneic CML is apparently due to the absence of Kk and is thus a failure of associative recognition. Results suggest a new mechanism of escape of T cell surveillance by leukemic cells which involves selective decrease of the H-2Kk antigens, which in this and other studies, have been shown to serve as elements of associative recognition in Gross virus leukemia. (6 Refs)

44. IMMUNOTHERAPY OF METASTASES OF HUMAN NEOPLASTIC CELLS GROWN IN IMMUNODEFICIENT MICE.

Lozzio BB, Machado EA, Lozzio CB, Mitchell J, Wust CJ
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Cancer Immunol Immunother; 12(2):135-140 1982

Incidence and extension of metastasis were determined in nude mice with spleens and in BALB/c lasat mice without spleens after inoculation of K-562 human leukemia cells to determine the effectiveness of antibody to K-562 cells as an immunotherapeutic agent. Since the cumulative incidence of metastases was nearly identical in both nude and lasat mice and since the presence of the spleen solely appeared to influence the incidence of brain and lymphatic metastases, experiments were performed in nude mice. Metastases were found in untreated mice between 10 and 115 days of age. The administration of normal gammaglobulin did not modify the overall incidence and random pattern of the metastatic process. Nude mice challenged neonatally with K-562 cells and treated with immune gammaglobulin had small intravascular emboli of K-562 cells. Only one or two emboli in each lung were found in a large number serial sections. Extravasation of the malignant cells in the lung and metastases in other organs were not observed. Histological examinations of serial sections demonstrated that pulmonary accumulations of K-562 cells in neoplastic emboli, micrometastases, and metastases could be distinguished.

Mice treated with immune gammaglobulin had significant augmentation of the total WBC count due to absolute increase in the number of lymphocytes and monocytes. Effects of normal vs immune gammaglobulin on hematologic parameters was not dependent on injection of K-562 cells. In absorbed goat immune serum, 34-40% of the total proteins was gammaglobulin as compared with 12-15% in preimmune goat serum. The difference (15-16 mg/ml) was considered to be immune IgG. (28 Refs)

45. GROWTH OF CANINE TUMORS TRANSPLANTED INTO NORMAL ADULT DOGS IMMUNOSUPPRESSED BY CYCLOSPORIN A.

Deeg HJ, Hackman RC, Weiden PL, Storb R
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Cancer Immunol Immunother; 12(2):147-152 1982

The ability of implanted neoplasms that had arisen spontaneously in unrelated dogs to grow was examined in beagles and mongrels treated with cyclosporin A (CyA). Five of six osteogenic sarcomas (OS) and the single thyroid carcinoma, transplanted in the form of minced pieces, proliferated into macroscopic tumors measuring up to 6 x 6 x 7 cm in dogs immunosuppressed with CyA. Stopping CyA led to spontaneous regression of all tumors except one OS. The tumor persisted at approx the same size. At the time of euthanasia 40 days after stopping CyA, there was no evidence of tumor rejection. Biopsies obtained during administration of CyA showed sc tumor invasion with very little or no associated inflammatory infiltrates. OS implants sometimes developed central necrosis with neutrophilic infiltration. Following CyA discontinuation, large numbers of lymphocytes and a few plasma cells surrounded and peripherally infiltrated tumor nests. Necrosis of many individual tumor cells was observed in areas of inflammation. None of the four transplanted lymphomas or the mastocytoma produced tumors. Lymphocyte proliferation was suppressed in sera from CyA-treated dogs. The results indicated that immunosuppression by CyA allowed transplantation of spontaneously occurring canine solid tumors into normal dogs. Tumor growth was most likely mediated by inhibition of host T cells and was reversible upon discontinuation of CyA treatment. (27 Refs)

46. IN VIVO ASSESSMENT OF IMMUNOTOXICITY.

Munson AE, Sanders VM, Douglas KA, Sain LE, Kauffmann BM, White KL
Dept. Pharmacology, Medical Coll. Virginia, Richmond, VA, 23298
Environ Health Perspect; 43:41-52 1982

A basic toxicological approach is described for assessing the risk of a chemical perturbing the immune system. CD-1 mice were exposed for 14 or 90 days to one of several chlorinated hydrocarbons: 1,2-dichloroethane, 1,2-dichloroethylene or 1,1,2-trichloroethylene. Other mice were exposed to dexamethasone, a known immunosuppressive agent. The immune system is evaluated against a background of the more standard toxicological parameters such as fluid consumption, body and organ weights, hematology, clinical chemistry, and blood coagulation. Reported here are the results for the male mice after 14-day exposure to three chlorinated hydrocarbons and after 90-day exposure to 1,2-dichloroethane and dexamethasone. Acute toxicity studies were performed to provide a basis for doses used in the subchronic studies. The LD50 values are reported. The status of the humoral immune system was determined by measuring the number of IgM spleen antibody-forming cells to sRBC, the serum antibody level to sRBC, and the lymphocyte response to the B-cell mitogen, LPS. The data suggest that dexamethasone administered in the drinking water in nonspecifically cytotoxic to the spleen cells. Cell-mediated immunity was assessed by measuring the DTH response to sRBC and the response to the T-lymphocyte mitogen, concanavalin A. Dichloroethane did not alter the functional activity of the reticuloendothelial system, as measured by the vascular clearance rate and tissue uptake of 51Cr sRBC. In the case of dexamethasone exposure, only the spleen and thymus showed decreased uptake of 51Cr sRBC, which was directly related to decrease in size. The approaches and results from these types of studies provide a basis for judging a chemical's potential risk to the immune system. (7 Refs)

47. INDUCTION OR ELIMINATION OF TUMOR-SPECIFIC IMMUNITY AGAINST A CHEMICALLY-INDUCED RAT TUMOR USING AUTO-ANTI-IDIOTYPIC IMMUNITY.

Binz H, Meier B, Wigzell H
Inst. Immunology and Virology, Univ. Zurich, CH-8028 Zurich, Switzerland
Int J Cancer; 29(4):417-423 1982

DA rat sarcomas P1 and P2 were induced by dimethylbenz(a)anthracene. A tumor-specific immune response of DA rats against P1-tumor cells could be demonstrated at the humoral and cellular level. DA anti-P1 antibodies were purified on fixed P1-tumor cells and used as autoimmunogen in DA rats for the production of anti-idiotypic antibodies. Such anti-idiotypic antibodies could be demonstrated by using a solid-phase radioimmunoassay and by their ability to induce secondary type of DA anti-P1 responses in vitro. In addition, such antibodies were able to induce cytotoxic T lymphocytes capable of eliminating P1-tumor cells but not control tumor cells. In some of the auto-immunized DA rats enhanced P1-tumor growth could be observed, indicating that the anti-idiotypic immune response had led to a selective ablation of idiotypic, potential anti-P1 reactive T cells. (Author abstract) (30 Refs)

48. CELL-MEDIATED IMMUNITY TO VIRAL PROTEINS IN MICE BEARING MOLONEY SARCOMAS.

Koppi TA, Halliday WJ
Dept. Microbiology, Univ. Queensland, St. Lucia, Queensland 4067, Australia
Immunol Lett; 4(3):135-140 1982

Definition of the soluble antigens responsible for in vitro reactivity in the leukocyte adherence inhibition (LAI) assay was studied with extracts and purified viral proteins. Viral proteins were tested in various concentrations with peritoneal cells (PC) from mice bearing tumors induced by Moloney sarcoma virus (MSV). The LAI indicated weak reaction with viral proteins p10 and p12, and significant adherence with gp71 and p30. In order to assess whether blocking factors could be directed against LAI with viral proteins, the normal serum in virus-induced LAI was replaced by serum from tumor-bearing mice. Results with tumor extract, gp71 and p30 showed that LAI was blocked. The effect of depletion of macrophages on the indirect LAI was tested with a MSV tumor extract and the viral protein gp71. Unfractionated PC reacted with both the extract and gp71. Nonadherent cells (lymphocytes) were not reactive with either source of antigen, indicating a requirement for adherent cells (macrophages). These accessory cells could be replaced by normal PC to give restored reactivity. Thus, a non-viral tumor-associated antigen was the active component of the extract. LAI reactivity with both tumor extract and gp71 depended on the presence of accessory adherent cells. (31 Refs)

49. EFFECT OF BENZENE METABOLITES ON PHYTOHEMAGGLUTININ-STIMULATED LYMPHOPOIESIS IN RAT BONE MARROW.

Pfeifer RW, Irons RD
Dept. Pathology, Chemical Industry Inst. Toxicology, Research Triangle Park, NC
J Reticuloendothel Soc; 31(2):155-170 1982

Chronic exposure of animals to benzene results in lymphocytopenia and bone marrow depression. A highly sensitive microculture system was developed to amplify and characterize marrow mitogen response which depended on the isolation of cells by Percoll continuous density gradient centrifugation and strict adherence to optimal culture conditions. Maximal mitogen responses to phytohemagglutinin (PHA) and concanavalin A (con A), as assessed by (3H)-thymidine uptake, occurred at later times in rat bone marrow cultures (Days 5-7 of culture) compared with spleen and thymus (Days 2-3). Compared with spleen and thymus, the PHA:con A stimulation ratio was inverted for marrow, yet the responsive cells were morphologically identical to those of peripheral lymphoid organs. Populations enriched in lymphoid precursors were inhibited from responding to PHA stimulation at noncytotoxic concentrations (greater than uM) of the benzene metabolites, p-benzoquinone or 1,2,4-benzenetriol. Pretreatment with less than uM concentrations of metabolites resulted in a modulation of lectin-induced responses such that blastogenesis was induced at higher concentrations of lectin relative to untreated cells. These changes indicate that known metabolites of benzene induce a concentration dependent modulation of differentiation and proliferation in lectin-stimulated cells from rat bone marrow in vitro. (Author abstract) (56 Refs)

50. IMMUNE SELECTION OF TUMOR CELL VARIANTS IN CHICKENS BEARING TUMORS INDUCED BY AVIAN SARCOMA VIRUS.

Wainberg MA, Israel E, Yu M
Lady Davis Inst. for Medical Res., Sir Mortimer B. Davis-Jewish General Hosp., Montreal, H3T 1E2 Quebec, Canada
Cancer Res; 42(5):1669-1675 1982

We have compared avian sarcoma cells, cultured from tumors at various stages of growth, in terms of their ability to synthesize infectious progeny virus and to express antigens that are reactive with the sensitized lymphocytes of tumor-bearing host. Cell-mediated immunity in chickens bearing tumors induced by avian sarcoma viruses was monitored by each of a target cell cytotoxicity test and an antigen-driven lymphocyte stimulation assay. Our results show that it is only those tumor cells which have been derived from progressively growing neoplasms that are able to synthesize infectious progeny virus and to specifically interact with the sensitized lymphocytes of tumor-bearing hosts. In contrast, cells from regressing tumors do not express relevant antigens to the same extent as do progressors, and they synthesize noninfectious particles only. Experiments on cellular outgrowths, derived from the plating at limited dilution of progressively growing tumor cells, revealed that such producers of defective virus are present at the earliest stages of tumor growth. Both these cells and regressing tumor cells are poorly stained (about 10%) in indirect immunofluorescence tests by antiserum against viral envelope glycoprotein, whereas tumor cell from progressing neoplasms react well (about 60 to 85%). These results suggest that tumor cells which are found in regressing neoplasms are selected out by a functional immune response directed against cells which are efficient producers of progeny virus. (Author abstract) (24 Refs)

51. INVOLVEMENT OF T-LYMPHOCYTES IN THE STIMULATORY EFFECTS OF EMT6 TUMORS ON MEDULLARY PLURIPOTENT STEM CELLS OF BALB/C MICE.

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Cancer Res; 42(5):1922-1926 1982

Untreated EMT6 tumors and bone marrow of tumor-bearing BALB/c mice secrete factors capable of stimulating quiescent medullary splenic colony-forming units into cycle. Since the tumor population is heterogenous, it is of interest to determine the nature of the cells which are involved in this phenomenon. Experiments with conditioned media from tumors of BALB/c and athymic mice show that EMT6 cells themselves may secrete a stimulating factor but that the presence of T-lymphocytes is necessary at some time in the development of the tumor. Likewise, the presence of the tumor is necessary for bone marrow to secrete these factors in our experimental model. This suggests reciprocal influences of the T-cells and the EMT6 tumor cells in the phenomena that we describe. (Author abstract) (36 Refs)

52. EFFECT OF MOUSE HEPATITIS VIRUS INFECTION ON 'NATURAL KILLER CELL' ACTIVITY IN NUDE MICE.

Tamura T, Sakaguchi A, Ishida T, Fujiwara K
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Microbiol Immunol; 25(12):1363-1368 1981

The effects of the NuU strain of mouse hepatitis virus (MHV) on natural kill (NK) cells was studied in male nude (nu/nu) and female heterozygous (nu/+) mice with a BALB/c background. NK cell activity of spleens from MHV-infected nu/nu and nu/+ mice was determined in microtiter wells with 10(4) radio-labeled cells of different established cell lines (DBT, L-929, RL male-1 [RL], or YAC-1). The cytotoxicity of spleen cells from nu/+ against Yac-1 and RL cells was markedly elevated at 1 and 4 days after ip infection with MHV-Nu, and decreased thereafter. In nu/nu cells, significant toxicity against DBT cells was seen only 1 day after infection and activity was low at 4 days or later. No cytotoxicity was found in either nu/nu or nu/+ cells. Since NK activity seemed to be enhanced after MHV infection in both nu/nu and nu/+ cells, the effective cell population was determined with spleen cells from nu/nu mice 24 hr after infection with MHV. Spleen cells passed through Sephadex G-10 showed high cytotoxicity for all target cells comparable to that of whole preparations. Depletion of B cells significantly increased toxicity, while that of adherent cells was low. Titers of 1:1,000 to 1:2,000 of interferon (IFN) were detected until 2 days after infection in both nu/nu and nu/+ mice. In another study, nu/nu mice were injected ip with either UV-irradiated nu/+ spleen homogenate having an IFN titer of 1:800, or with UV-inactivated MHV, and spleen cells were examined for NK activity 24 hr later. Neither the transfer of infected nu/+ spleen homogenate nor the injection of UV-inactivated MHV affected NK activity. The NK activity increased throughout the course of MHV infection, but transferred IFN had no effect on NK activity. (19 Refs)

53. REGULATION OF NATURAL KILLER ACTIVITY IN VIVO: PART IV - HIGH NATURAL KILLER ACTIVITY IN ALCOHOL DRINKING MICE.

Saxena QB, Saxena RK, Adler WH
Clinical Immunology Section, Gerontology Res. Center, Natl. Inst. on Aging, NIH, Baltimore, MD, 21224
Indian J Exp Biol; 19(11):1001-1006 1981

An increase in natural killer (NK) activity was observed in spleen cells of alcohol drinking (2%, 4%, 8%, or 16% alcohol vol/vol in water) mice compared with control mice. The increase was maximal in mice given 16% alcohol-water. No enhanced NK activity was observed in mice given 10% alcohol for 2 or 8 days, while a 2-3-fold increase was observed in those given alcohol for 4-6 wk. Cells responsible for the increased NK activity in alcohol drinking mice were not T-cell, B-cell, or macrophage populations. (16 Refs)

54. LYMPHOTOXIN ENHANCES THE SUSCEPTIBILITY OF NEOPLASTIC AND PRENEOPLASTIC CELLS TO NATURAL KILLER CELL MEDIATED DESTRUCTION.

Ransom JH, Evans CH
Tumor Biology Section, Lab. Biology, Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205
Int J Cancer; 29(4):451-458 1982

Treatment of neoplastic guinea-pig cells for 1-14 days with 300 units of guinea-pig lymphotoxin/ml medium enhanced two- to five-fold their susceptibility to natural killer (NK) cell-mediated cytotoxicity as measured by 4 hr 51Cr and 72 hr [3H]-thymidine-release assays. The NK susceptibility of human neoplastic and guinea-pig non-neoplastic cells refractory to guinea-pig lymphotoxin growth-inhibitory activity was unchanged after lymphotoxin treatment. Lymphotoxin preparations were free of detectable interferon and the enhancing activity copurified with lymphotoxin during diafiltration and isoelectric focusing. Treatment of NK cells with lymphotoxin preparations also augmented NK-mediated lysis but that activity did not copurify with lymphotoxin. As with neoplastic cells, lymphotoxin-sensitive preneoplastic cells previously treated with ultraviolet light, a chemical carcinogen, or carcinogen and the tumor-promoting agent tetradecanoyl-phorbol-acetate also exhibited lymphotoxin enhancement to NK-cell destruction. Thus, the immunologic hormone lymphotoxin enhances the susceptibility of lymphotoxin-sensitive cells to NK-cell destruction, indicating that these two natural immune mediators, lymphotoxin and NK cells, have the potential in concert to regulate carcinogenesis and neoplastic growth. (Author abstract) (30 Refs)

55. IMPAIRMENT OF SPLENIC NATURAL KILLER CELL ACTIVITY OF MICE INFECTED WITH THE POLYCYTHEMIC STRAIN OF FRIEND LEUKEMIA VIRUS.

Migliorati G, Jezzi T, Favalli C, Garaci E, Rossi RB, Bonmassar E
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Cancer Immunol Immunother; 12(2):177-179 1982

The effect of polycythemic strain Friend leukemia virus (FLV-P) infection on natural killer (NK) activity in FLV-P-susceptible DBA/2 inbred mouse recipients was examined. Spleen cells were collected from 4-wk-old control or FLV-P-infected donors on days 2, 7, 14, 21, and 28 after virus inoculation. Pools of four spleens each were tested for NK activity at various attacker:target ratios. A significant decrease of NK activity occurred as early as 7 days after infection. From day 14 onward, splenic NK function of infected mice was minimal. Moreover, an actual decrease of NK activity of the whole spleen occurred in these mice, as evidenced by the extremely low levels of lytic units per spleen detectable 3 wk after FLV-P infection. A limited but progressive decline of NK activity was found in the spleen of control non-infected donors, presumably expressing an age-dependent decrease of NK levels in the organ. The mechanism of suppression is discussed. It was suggested that suppression could be based on cell-mediated impairment of NK effector function, or on antigenic competition from splenocytes expressing NK antigens elicited by FLV-P. (19 Refs)

56. MUTAGENIC AND TUMOURIGENIC PROPERTIES OF THE SPORES OF ASPERGILLUS CLAVATUS.

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Dept. Botany, Univ. Edinburgh, King's Building, Edinburgh EH9 3JH, England
Br J Cancer; 45(1):105-117 1982

Spore walls of a sputum-derived isolate of Aspergillus clavatus yielded mutagen(s) when their extracts were fractionally precipitated with ethanol following alkaline hydrolysis. After spores were given by nasal inoculation to 6-8-wk-old CF-1 mice, light and electron microscopy of lung sections showed that they had been readily phagocytosed by the polymorphonuclear leukocytes and alveolar macrophages mobilized during early allergic alveolitis in immunized mice. The formation of phagosomes was followed in thioglycollate-stimulated peritoneal macrophages grown in vitro. Unimmunized mice showed a comparable lung reaction, attributed to pulmonary mycotoxicosis, and revealed a rising incidence of lung tumors, from 25% at 2 months from inoculation, to 27.3% at 6 and to 55.5% at 8. Mean numbers of tumors per lung rose from 1.0 to 2.2. Total tumors, including lymphomas, reached a final incidence of 77.7% at 8 months, when control animals were tumor-free. Tumor development correlated with the retention of apparently intact spores within giant cells probably derived from aggregates of alveolar macrophages. The implications of these findings in the light of the known history of human exposure to such spores is discussed. (Author abstract) (34 Refs)

57. CIMETIDINE AMPLIFIES THE ANTI-NEOPLASTIC EFFECT OF TRICHINELLA SPIRALIS IN MICE.

Ruitenberg EJ, Kruizinga W, Steerenberg PA, Elgersma A, De Jong WH
Lab. Pathology, Natl. Inst. Public Health, Bilthoven, The Netherlands
Br J Cancer; 45(2):314-316 1982

The possible involvement of histamine in the antineoplastic effect of Trichinella spiralis on growth of a murine fibrosarcoma (induced by 3-methylcholanthrene) was investigated. An H2-receptor antagonist (cimetidine) and an H2-receptor agonist (tolazoline) were used. Inbred female BALB/c mice were infected orally with 200 T spiralis larvae 8 days before sc inoculation of 5 x 10(5) tumor cells into the footpad. Cimetidine (50 mg/kg) or tolazoline HCl (0.5 mg/kg) was administered ip on days-8,-6,-4,-2, and 0. Preinfection with 200 T spiralis larvae retarded tumor growth as early as 5 days after tumor cell inoculation. Cimetidine caused an additional tumor growth retardation visible from day 5. Tolazoline did not affect tumor retardation induced by T spiralis. Neither drug alone affected tumor growth. The antitumor effect of T spiralis may be modulated by parasite-induced suppressor T cells, known to possess H2-receptors, whose effect is blocked by cimetidine. The potential of cimetidine in regulating immune responses, including its role in cancer immunotherapy, is implied by the findings. (8 Refs)

58. ANTIGEN-SPECIFIC PRODUCTION OF IMMUNE INTERFERON BY T CELL LINES.

McKimm-Breschkin JL, Mottram PL, Thomas WR, Miller JF
Walter and Eliza Hall Inst. for Medical Res., Royal Melbourne Hosp., Victoria 3050, Australia
J Exp Med; 155(4):1204-1209 1982

The ability of antigen to induce production of immune gamma-interferon (IFN-g) in two continuous T cell lines that mediate hapten-specific delayed hypersensitivity to oxazolone was investigated. Both cell lines produced IFN-g after stimulation by specific antigen and the IFN-g was restricted by the I region of the major histocompatibility complex.The antiviral activity was species specific, stable at 56 C for 30 min. and totally inactivated by treatment at pH 2 and by treatment with 100 ug/ml of trypsin. (13 Refs)

59. CYTOTOXIC T LYMPHOCYTES PRODUCE IMMUNE INTERFERON IN RESPONSE TO ANTIGEN OR MITOGEN.

Klein JR, Raulet DH, Pasternack MS, Bevan MJ
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Exp Med; 155(4):1198-1203 1982

When cultured with concanavalin A or with allogeneic cells presenting antigen, clones of murine antigen-specific, H-2-restricted cytotoxic T lymphocytes (CTL) released high levels of immune interferon (IF). Release of IF by cloned cultures with allogeneic cells was antigen specific and H-2 restricted. Thus, CTL can deliver a 'one-two punch' at a local site involving death to a target cell and the local release of immune IF. (23 Refs)

60. EFFECT OF PROSTAGLANDINS ON ELICITATION OF ANTI-VIRAL CYTOLYTIC ACTIVITY.

Hale AH, Evans DL, Daniel LW
(c/o Daniel) Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC, 27103
Immunol Lett; 4(3):171-174 1982

The modulating effect of prostaglandins (PG) E1 and E2 on the elicitation of secondary anti-vesicular stomatitis virus (VSV) cytotoxic T-lymphocytes (CTL) with viral antigens was studied. Results indicate both PGE1 and PGE2 inhibit induction of anti-VSV CTLs by UV-inactivated VSV. In the presence of indomethacin, VSV CTL activity was augmented. Results suggest prostaglandins may modulate anti-viral CTL responses. (16 Refs)

61. PROSTAGLANDIN E2-MEDIATED ENHANCEMENT OF HUMAN PLASMA CELL DIFFERENTIATION.

Lydyard PM, Brostoff J, Hudspith BN, Parry H
Dept. Immunology, Middlesex Hosp. Medical Sch., London W1, England
Immunol Lett; 4(3):113-116 1982

Addition of prostaglandin E2 (PGE2) to cultures of lymphocytes from normal subjects enhanced plasma cell differentiation in the presence of pokeweed mitogen (PWM). T-cell mitogenesis to concanavalin A was inhibited with the same concentrations of PGE2. PGE2 failed to enhance plasma cell (PC) differentiation of lymphocytes from patients with systemic lupus erythematosus. Indomethacin in the presence of PWM suppressed PC differentiation in 2/4 experiments. (23 Refs)

62. AUGMENTATION OF THE ANTI-TUMOR THERAPEUTIC EFFICACY OF LONG-TERM CULTURED T LYMPHOCYTES BY IN VIVO ADMINISTRATION OF PURIFIED INTERLEUKIN 2.

Cheever MA, Greenberg PD, Fefer A, Gillis S
Div. Oncology, RK-25, BB1015 Health Sciences, Univ. Washington, Seattle, WA, 98195
J Exp Med; 155(4):968-980 1982

C57BL/6 mice bearing disseminated FBL-3 (a transplanted ascitic Friend's virus-induced leukemia) were treated with cyclophosphamide (CY: 180 mg/kg) and long-term cultured T lymphocytes (CTL) plus purified interleukin 2 (IL-2: 80 units/day). The long-term cultured T lymphocytes were highly cytotoxic to FBL-3, but not to an antigenically distinct C57BL tumor, EL-4(G-). CTL continued to proliferate in vitro and expand in number when repeatedly exposed to IL-2 in vitro; however, when cultured without IL-2, less than 10% remained viable at 72 hr. Gamma-irradiation reduced the number of viable cells to less than 5% at 72 hr, even in the presence of IL-2. When IL-2 was administered in vivo to mice with FBL-3 tumors, no detectable antitumor effect was observed, even with CY. Therapy on day 5 after tumor inoculation with CY plus CTL (5 x 10(6)) prolonged survival of mice but produced no cures. Treatment with CY plus CTL plus IL-2 on days 5-9 cured 11/16 mice. Thus, as an adjunct to CY, CTL were effective in tumor therapy, and their efficacy was significantly augmented by inoculation of exogenous IL-2. The in vivo efficacy of exogenous IL-2 in adoptive chemoimmunotherapy required that the effector cell be capable of proliferating in the host. While noncultured immune cells were effective in antitumor therapy, their efficacy was not augmented by exogenous IL-2. It is suggested that IL-2 promotes in vivo growth and/or survival of adoptively transferred cells. (41 Refs)

63. MECHANISM OF T CELL ACTIVATION: ROLE AND FUNCTIONAL RELATIONSHIP OF HLA-DR ANTIGENS AND INTERLEUKINS.

Palacios R
Dept. Immunobiology, Wallenberglaboratory, Karolinska Inst., Lilla Frescati, S-104 05 Stockholm 50, Sweden
Immunol Rev; 63:73-110 1982

The mechanism by which non-activated T-lymphocytes become sensitive to interleukin 2 (IL2) is reviewed. T cells appear to be sensitized to IL 2 during activation by HLA-DR antigens by the induction of IL-2 receptors, which occurs when foreign antigen from antigen-presenting cells plus HLA-DR molecules interact with the corresponding T cell receptors. Studies on the control of IL-2 synthesis are reviewed in various systems. (83 Refs)

64. INTERLEUKIN 1 AND T CELL ACTIVATION.

Mizel SB
Microbiology Program, Pennsylvania State Univ., University Park, PA, 16802
Immunol Rev; 63:51-72 1982

The characterization and role of interleukin 1 (IL 1) in T cell activation is reviewed. IL 1 appears to be the macrophage-derived mediator needed to initiate and amplify all T cell-dependent immune responses and to induce inflammatory mediators. IL 1 also induces the synthesis and secretion of interleukin 2, which is an essential element for T cell activation involving converting a primary maturational signal from macrophages into a secondary proliferative signal from T cells. (62 Refs)

65. MODULATION OF THE IMMUNE RESPONSE BY PLASMA PROTEASE INHIBITORS. I. ALPHA2-MACROGLOBULIN AND ALPHA1-ANTITRYPSIN INHIBIT NATURAL KILLING AND ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY.

Ades EW, Hinson A, Chapuis-Cellier C, Arnaud P
Dept. Immunology, Lilly Res. Lab., 307 E. McCarty St., Indianapolis, IN, 46285
Scand J Immunol; 15(1):109-113 1982

The two major protease inhibitors in human serum, alpha1-antitrypsin (alpha1AT) and alpha2-macroglobulin (alpha2m), were analyzed for their effects on antibody-dependent cell-mediated cytotoxicity (ADCC) and natural killing (NK). The results indicate that both alpha1AT and alpha2m decrease ADCC and NK in a dose-responsive pattern. (Author abstract) (24 Refs)

66. ANALYSIS OF UNEXPECTED INHIBITIONS OF T LYMPHOCYTE PROLIFERATION TO SOLUBLE ANTIGEN, ALLOANTIGEN AND MITOGEN BY UNFRAGMENTED ANTI-I-AK OR ANTI-I-E/CK MONOCLONAL ANTIBODIES.

Dubreuil PC, Caillol DH, Lemonnier FA
Centre d'Immunologie INSERM-CNRS de Marseille-Luminy, Case 906, 13288 Marseille Cedex 9, France
J Immunogenet; 9(1):11-24 1982

Monoclonal antibodies (mAb) against I-Ak and I-E/Ck were tested for effects on T lymphocyte proliferative responses to keyhole limpet hemocyanin (KLH: a soluble antigen), mixed lymphocyte response (MLR) induced by allogeneic differences (alloantigens), and proliferative response of purified T cells to concanavalin A (Con A: a mitogen). The mAb partially inhibited KLH-induced proliferation and appeared to be directed at the antigen-specific response. The inhibition was not due to reduction of a fetal calf serum effect, was specific for anti-Ia mAb, and did not result from a non-specific toxic effect on T lymphocyte destruction. The mAb inhibited proliferative responses to the non-H-2 Mls locus, the whole H-2 locus, and the K subregion, even though the stimulating alloantigens were not I region-encoded. The mAb also inhibited Con A response of H-2k but not H-2b accessory cells. Results suggest that I region restriction of corresponding antigen presentation to T cells is not necessarily indicated by in vitro inhibition of T cell proliferative response by anti-Ia antibodies. (35 Refs)

67. INHIBITION OF THE LYMPHOCYTE BLASTOGENIC RESPONSE TO ANTIGEN BY SERUM-FREE CULTURE SUPERNATANTS OF LEUKEMIC B CELLS.

Walsh JD, Geczy CL
Kolling Inst. Medical Res., Royal North Shore Hosp. Sydney, New South Wales 2065, Australia
Cell Immunol; 67(2):241-254 1982

Suppressive factors were detected in culture supernatants of the guinea pig B-cell L2C leukemia. Dialyzed culture supernatants (DCS) inhibited the blastogenic response of sensitized lymph node cells (LNC) to a wide dose range of the sensitizing antigen (ovalbumin or PPD) but failed to inhibit the proliferative response to PHA or Con A. In addition, DCS inhibited the response of blast cells to preformed T-cell growth factor (TCGF). The inhibitor(s) in DCS was noncytotoxic, heat stable (30 min at 80 C), resistant to treatment with trypsin, and exerted its effect subsequent to activation of sensitized LNC by antigen. Washing of DCS-treated cells restored normal reactivity to a subsequent antigen challenge. The target cell for the inhibitor may be cells responding to amplification signals produced by activated T cells. KCl (3 M) extracts of L2C cells behaved like DCS in inhibiting only antigen responses. Both undialyzed culture supernatants (UCS) and leukemic sera inhibited mitogen, allogeneic, and antigen-stimulated proliferative responses by greater than 80%. These soluble factors may participate in the depression of cell-mediated immunity associated with lymphoid malignancies. (Author abstract) (36 Refs)

68. REGULATION OF THE IMMUNE RESPONSE BY THE FC PORTION OF IMMUNOGLOBULIN.

Morgan EL, Thoman ML, Weigle WO
Dept. Immunopathology, Scripps Clinic and Res. Foundation, 10666 N. Torrey Pines Road, La Jolla, CA, 92037
Protides Biol Fluid Proc Colloq; 29:401-404 1982

Studies are presented which indicate that the Fc portion of mammalian immunoglobulin possesses the ability to augment in vivo and in vitro specific antibody responses and in vitro T cell-mediated immune responses. Enhancement only occurs with thymus-dependent antigens. Although Fc fragments do not induce T cells to proliferate, they enhance antigen and allogeneic cell-induced proliferation, acting only on cell populations with the Lyt 1+2-phenotype. Fc fragments also potentiate primary cell mediated lympholysis response. (11 Refs)

69. STIMULATION OF HUMAN MONOCYTE CHEMOTAXIS BY ANTI-BETA2-MICROGLOBULIN.

Conway TP, Poulik MD
Dept. Biological Sciences, Northern Illinois Univ., DeKalb, IL
Protides Biol Fluid Proc Colloq; 29:201-204 1982

Chemotactic stimulation of human monocytes by anti-beta2-microglobulin (anti-B2m) and its fragments was studied with a modified Boyden assay. Both rabbit and goat anti-B2m stimulated directional migration of human peripheral blood monocytes. Whether anti-B2m is a chemotaxin or a chemokinin remains uncertain, although incubation of anti-B2m and monocytes in the absence of a concentration gradient reduced cell movement. The Fc region of IgG or aggregation of cell membrane proteins was not required for stimulation of movement since anti-B2m F(ab')2 and Fab' fragments were chemotactic. (20 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

70. HUMAN MONOCLONAL AUTOIMMUNE ANTIBODY PRODUCED IN VITRO: RHEUMATOID FACTOR GENERATED BY EPSTEIN-BARR VIRUS-TRANSFORMED CELL LINE.

Steinitz M, Tamir S
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Eur J Immunol; 12(2):126-133 1982

The infection of selected lymphocytes from a rheumatoid arthritis patient with Epstein-Barr virus resulted in an immortalized cell line that secretes a monoclonal rheumatoid factor (RF). The cloned line has been growing for more than 24 mo, and constantly produces a monoclonal IgM,lambda, 19S, RF (1-2 ug/ml/10(6) cells). The RF agglutinates human and rabbit IgG (but not IgM) and also protein A-coated erythrocytes, but fails to do so to mouse, goat and swine IgG-coated erythrocytes. When bound to immune complexes, this monoclonal RF does not bind complement. In the cell supernatant RF is the only immunoglobulin and it comprises approx 5% of the total proteins. The affinity of RF to aggregated human IgG, as detected in inhibition experiments, is higher than that of Fc receptors found on human non-T lymphocytes, K562 and Daudi cell lines. (Author abstract) (44 Refs)

71. ACTIVATION OF NATURAL KILLER CELLS AND INDUCTION OF INTERFERON AFTER INJECTION OF MOUSE HEPATITIS VIRUS TYPE 3 IN MICE.

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Infect Immun; 35(3):869-873 1982

High levels of natural killer (NK) cell activity and high titers of interferon were observed in the peritoneal exudate of C57BL/6 mice 20 to 50 h after injection of mouse hepatitis virus Type 3 (MHV3) but not during the first 10 h after infection. C57BL/6 mice were susceptible to MHV3 infection and showed high titers of MHV3 in the peritoneal exudate 48 h after infection. A/J mice, in contrast, were resistant to the dose that killed 100% of the C57BL/6 mice (10 macrophage-infecting doses) and showed considerably lower virus titers than those shown by C57BL/6 mice. NK cell activity and interferon titers were significantly lower in the peritoneal exudate of A/J mice than in that of C57BL/6 mice. Serum interferon titers were also lower in A/J mice. Thus, our data show an inverse relationship between resistance and the levels of these two parameters. The data suggest that, in contrast to the situation observed with certain herpesviruses, interferon and NK cells may not be of overwhelming importance in the defense of mice against MNV3. (Author abstract) (14 Refs)

72. EPSTEIN-BARR VIRUS INCREASES THE PROLIFERATIVE RESPONSE AND THE GENERATION OF SUPPRESSOR AND CYTOTOXIC T-CELL FUNCTIONS IN AUTOLOGOUS MIXED LYMPHOCYTE REACTION.

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Scand J Immunol; 15(1):17-24 1982

Epstein-Barr virus (EBV) infection of stimulator cells significantly increased the proliferative response of T cells in the autologous mixed lymphocyte reaction (AMLR). The addition of a monoclonal anti-HLA-DR antibody to AMLR cultures in which either EBV-infected or non-infected non-T cells were used as stimulator cells strongly inhibited the proliferative response irrespective of the presence of EBV. It is concluded that EBV does not by itself activate the responding cells and that HLA-DR antigens are necessary to trigger T cells. Increased generation of suppressor T cells, determined in both alloantigen-induced DNA synthesis and pokeweed-mitogen-stimulated immunoglobulin production, was found after an EBV infection of stimulator cells. Similarly, EBV-infected non-T cells significantly increased the generation of killer T cells, determined in three different types of target cells: phytohemagglutinin-stimulated mononuclear cells, EBV-transformed cells, and concanavalin-A-activated murine spleen cells. The increased T-cell responses after an EBV infection may reflect the attempts in vivo to control and hold in check the viral infection. (Author abstract) (33 Refs)

73. SPLIT T-CELL TOLERANCE IN HERPES SIMPLEX VIRUS-INFECTED MICE AND ITS IMPLICATION FOR ANTI-VIRAL IMMUNITY.

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Dept. Pathology, Univ. Cambridge, Tennis Court Road, Cambridge, England

Immunology; 45(4):761-767 1982

Mice simultaneously injected intravenously and subcutaneously with herpes simplex virus fail to adoptively transfer delayed hypersensitivity (DH) to syngeneic recipients. The transferred lymph node cells also failed to rapidly eliminate infectious herpes from the pinna, despite the presence of cytotoxic T cells in the transferred suspension. Both primary and secondary cytotoxic cell responses in the draining lymph node were unaffected by the inhibition of DH. The lymph nodes from DH tolerized mice also contain lymphocytes capable of undergoing a proliferative response in vitro to herpes antigens. In addition, a neutralizing antibody response with IgG antibodies against herpes are also present in DH tolerized mice. These data suggest a form of split T-cell tolerance in which only DH responses are directly compromised. The implication of these findings for the pathogenesis of herpes simplex virus is discussed. (Author abstract) (13 Refs)

74. INFLUENCE OF H-2-LINKED GENES ON T CELL PROLIFERATIVE AND CYTOLYTIC RESPONSES TO PEPTIDES OF SENDAI VIRAL PROTEINS.

Miskimen JA, Guertin DP, Fan DP, David CS

Dept. Microbiology, Univ. Minnesota, Minneapolis, MN, 55455

J Immunol; 128(4):1522-1528 1982

Spleen cells from H-2 congenic mice were tested for their proliferative and/or cytolytic responses to partially purified products from CNBr cleavage of Sendai virus. In response to in vitro stimulation of Sendai-primed spleen cells with virus-infected cells, Sendai virus-specific cytolytic T lymphocytes restricted to H-2Kb, Kd, Kk, Ks, and Dd were generated. Of these H-2Kb- and Kd-, but not H-2Kk-, Ks-, and Dd-, restricted cytolytic T cells were generated after stimulation with partially purified Sendai peptides. H-2Dd-restricted, virus-specific cytotoxicity was generated in response to unseparated products from CNBr cleavage of Sendai virus. The pool of partially purified peptides contains some of the antigenic determinants that can stimulate a cytolytic response. These results suggest that each determinant on Sendai viral proteins may stimulate cytolytic T lymphocytes restricted to only a subset of the H-2K and D alleles which can be recognized by the sum of cytolytic T cells generated in response to all of the antigenic determinants on Sendai viral proteins. Thus, H-2K and D genes function as immune response genes regulating the cytolytic response to partially purified peptides and possibly to individual antigenic determinants on Sendai viral proteins. Only spleen cells from mice with the k haplotype in IA-IJ proliferate in response to partially purified peptides, whereas spleen cells from all three mice proliferate when virus is added to the cultures. These proliferating cells are sensitive to treatment with anti-Thy-1.2 and C, suggesting that immune response genes regulating T cell proliferative responses to individual viral determinants may also exist. (14 Refs)

75. THE EFFECTS OF T-CELL GROWTH FACTOR AND VIRUS PURIFICATION ON VIRUS-MEDIATED INHIBITION OF LYMPHOCYTE MITOGENESIS.

Wainberg MA, Margolese RG
Lady Davis Inst. Medical Res., Sir Mortimer B. Davis - Jewish General Hosp., 3755 Cote St. Catherine Road, Montreal, Quebec H3T 1E2, Canada
Clin Exp Immunol; 48(1):163-170 1982

Many different types of virus particles are able to non-specifically impede the ability of human peripheral blood lymphocytes to respond to mitogenic or alloantigenic stimuli. This result is not obtained if ultra-purified virus is employed, although virus which has been banded only once through sucrose generally retains inhibitory potential. Ultra-pure virus is relatively unable to bind to cell surfaces, suggesting the importance of physical contact between viruses and cells in order for the observed inhibition to occur. Addition of exogenous T-cell growth factor (TCGF) to cultures containing virus, cells and stimulus causes a dose-dependent reversal of the usual inhibitory effect. (Author abstract) (34 Refs)

76. CELL-MEDIATED IMMUNITY IN MALNOURISHED GUINEA PIGS AFTER MYCOBACTERIUM BOVIS BCG VACCINATION.

McMurray DN, Yetley EA
Dept. Medical Microbiology, Texas A and M Univ., College Station, TX, 77843
Infect Immun; 35(3):909-914 1982

Specific-pathogen-free guinea pigs were vaccinated with viable Mycobacterium bovis BCG and maintained on purified, isocaloric diets containing either 30% or 7.5% casein, or commercial chow. At intervals of 4, 5, 6, and 8 weeks postvaccination, groups of guinea pigs from each diet treatment were skin tested with purified protein derivative and killed. Protein-deficient animals exhibited progressive reductions in total serum proteins and albumin. Significantly greater numbers of viable M bovis BCG were recovered from the vaccination site and inguinal lymph nodes of protein-deficient guinea pigs at all intervals. In contrast, the development of delayed hypersensitivity was markedly retarded in the 7.5% casein group and was also reduced somewhat in the 30% casein group as compared to chow control. Peripheral blood lymphocytes from protein-deficient animals did not respond normally in vitro to a polyclonal T cell mitogen, phytohemagglutinin. These results demonstrate that protein-calorie malnutrition in this model impairs the development of cell-mediated immunity as evidenced by skin test anergy, lymphocyte hyporesponsiveness, and failure to control levels of viable M bovis BCG after vaccination. (Author abstract) (34 Refs)

77. EVIDENCE FOR HOST-MEDIATED ANTITUMOR ACTIVITY IN THE TREATMENT OF EXPERIMENTAL TUMOR WITH A HOT WATER EXTRACT FROM BCG.

Sato H, Arai H, Nagai H, Ito M, Satoh K, Kumano N, Motomiya M, Konno K
Dept. Internal Medicine, Res. Inst. Tuberculosis and Cancer, Tohoku Univ., Sendai 980, Japan
Tohoku J Exp Med; 136(1):67-74 1982

The mechanisms by which a hot water extract (HWE) of delipidated BCG shows antitumor activity when injected ip were investigated. Sarcoma 180 cells were injected in ddY mice and MH134 cells were injected in C3H/He mice. Incubation of tumor [illegible], with HWE for 120 min did not decrease cell visibility or prolong survival of hosts. IP injection of mice with small silica particles or carrageenan abrogated the HWE antitumor effects, indicating that these effects may be mediated by macrophages, since these substances are toxic to macrophages. IP injection of hydrocortisone acetate also reduced HWE activity, indicating that in addition to macrophages, some steroid-sensitive cells are involved in the antitumor activity. Simultaneous inoculation of tumor cells and peritoneal cells from HWE-injected mice reduced tumor growth. It appears that HWE ip injection results in host-mediated antitumor activity. (17 Refs)

78. EFFECT OF CERTAIN ANTIDEPRESSANT AGENTS AND THEIR COMBINATIONS WITH CYTOSTATICS ON TUMOR GROWTH AND ANTITUMORAL RESISTANCE.

Veksler IG, Riabukha VN, Andreeva NI, Polezhaeva AI, Mashkovskii MD, Balitskii KP
R. E. Kavetskii Inst. Problems in Oncology, Kiev, USSR
Eksp Onkol; 4(1):47-51 1982

Potential antineoplastic activity of antidepressant agents azaphen (AP) and pyrazidol (PZ) was studied in random-bred mice, C57Bl and BALB/c mice, random-bred rats, and rabbits with various induced and transplanted tumors. AP and PZ were administered in combination with cyclophosphamide (CP), thiophosphamide (TP), or benzo-TEPA. AP and PZ were administered ip at 10-25 mg/kg for 7-10 days. Neither AP nor PZ inhibited the growth of Guerin's carcinoma or Pliss' lymphosarcoma. AP provided a 29.4% inhibition of the growth of sarcoma 180, while PZ provided a 23.0-35.3% inhibition of the growth of sarcoma 180, methylcholanthrene-induced sarcoma, and colonic adenocarcinoma Ca755. PZ increased the lifespan and reduced the accumulation of ascitic fluid in mice bearing Ehrlich ascites carcinoma. AP and PZ enhanced the rate of tumor regression in BALB/c mice bearing Moloney sarcoma. AP and PZ stimulated the cellular immunity of tumor-bearing animals. AP and PZ enhanced the antineoplastic effect of cytostatic drugs. (23 Refs) (In RUS)

79. ACTIVATION OF MONOCYTE AND GRANULOCYTE ANTIBODY-DEPENDENT CYTOTOXICITY BY PHORBOL MYRISTATE ACETATE.

Klassen DK, Conkling PR, Sagone AL
Div. Hematology/Oncology, Ohio State Univ. Hosp., Columbus, OH, 43210
Infect Immun; 35(3):818-825 1982

We have characterized the effects of phorbol myristate acetate (PMA) on human monocyte and neutrophil oxidative metabolism and antibody-dependent cytotoxicity toward anti-D sensitized human erythrocytes (RBC) and a human lymphoblastoid cell line (CEM). Hexose monophosphate shunt activity was measured by [1-14C]glucose oxidation and target lysis by 51Cr release. PMA produced a dose-dependent stimulation of hexose monophosphate shunt activity. Neutrophils responded with higher hexose monophosphate shunt activity and at a lower PMA concentration than did monocytes. PMA increased monocyte lysis of antibody-sensitized RBC by two-thirds, but did not affect lysis of CEM targets. Neutrophils were unable to lyse either antibody-sensitized or nonsensitized RBC without the addition of PMA. When PMA was added, lysis of both targets increased markedly. Neutrophils without PMA were able to lyse a small number of both antibody-sensitized and nonsensitized CEM targets. PMA also increased neutrophil lysis of these targets. Target lysis by neutrophils from a patient with chronic granulomatous disease, cells unable to produce reactive oxygen species, was not increased by PMA. Chronic granulomatous disease monocytes, however, responded to PMA by more than doubling lysis of antibody-sensitized RBC. Hypoxia inhibited PMA augmentation of antibody-sensitized RBC lysis by neutrophils, but not by monocytes. Generation of reactive oxygen species by the xanthine-xanthine oxidase system inhibited CEM growth, but did not cause lysis, indicating that in some cases oxidative injury may be nonlytic. We suggest that PMA augments neutrophil cytotoxicity to tumor and RBC targets by stimulating reactive oxygen species-mediated lysis, but in monocytes augmentation of lysis is due to activation of a nonoxidative mechanism of lysis. (Author abstract) (43 Refs)

80. IDENTIFICATION OF PHORBOL ESTER RECEPTORS IN T-CELL GROWTH FACTOR-PRODUCING AND -NONPRODUCING EL4 MOUSE THYMOMA CELLS.

Sando JJ, Hilfiker ML, Piacentini MJ, Laufer TM

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Cancer Res; 42(5):1676-1680 1982

Two lines of EL4 mouse thymoma cells have been examined for the presence of specific phorbol ester-binding components. Both lines displayed saturable specific binding as determined by using [20-3H]phorbol 12,13-dibutyrate in a whole-cell-binding assay. Specific binding in each line was max within 10 min at 37 C but rapidly decreased to about 30% within 30 min. Max binding at 4 C was reached after 60 min and was stable for at least 8 hr; however, this level was only about 30% of the max obtained at 37 C. Saturation of the specific binding after 3 hr at 4 C occurred at a concentration (30 to 50 nM) which is consistent with that yielding max T-cell growth factor production in the responding line but greater than that at which inhibition of proliferation was detected in those cells. Scatchard analysis of these data was consistent with the existence of a single class of binding sites with a Kd of 11 +-0.6 (SD) nM for the T-cell growth factor-producing cells and 18 +-1.9 nM for the nonproducing line. The numbers of sites per cell measured in the responding and nonresponding lines were 5.6 +-1.3 x 10(4) and 7.1 +-0.2 x 10(4), respectively. Competition by a series of phorbol esters for [20-73 1H]phorbol 12,13-dibutyrate binding in the responding line showed the same order of potency as production of T-cell growth factor and inhibition of proliferation by the analogs. These data support identification of the phorbol ester-binding component in the responding cells as the receptor mediating T-cell growth factor production. The presence of binding components in unresponsive cells in numbers and with characteristics indistinguishable from those of responsive cells suggests that the failure to respond is due to modification of a step which succeeds the initial binding event. (29 Refs)

81. SPONTANEOUS CYTOTOXICITY.

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Aust J Exp Biol Med Sci; 59(6):681-694 1981

When mouse spleen cells were cultured in vitro without the deliberate addition of any stimulating cells, T cell-mediated cytotoxicity was generated which could be detected by lysis of 51Cr-labeled syngeneic and allogeneic tumor target cells. The clonal basis of such spontaneous cytotoxicity was investigated by limit dilution analysis and a comparison made between it and so-called 'tumor-specific' cytotoxicity generated in vitro. (Author abstract) (22 Refs)

82. SUPPRESSION OF NATURAL KILLING IN VITRO BY MONOCYTES AND POLYMORPHONUCLEAR LEUKOCYTES. REQUIREMENT FOR REACTIVE METABOLITES OF OXYGEN.

Seaman WE, Gindhart TD, Blackman MA, Dalal B, Talal N, Werb Z
Fort Miley Veterans Admin. Medical Center, San Francisco, CA
J Clin Invest; 69(4):876-888 1982

Natural killer cells spontaneously lyse certain tumor cells and may defend against malignancy. Natural killing (NK) by human peripheral blood mononuclear cells (PBMC) is suppressed in vitro by phorbol diester tumor promoters, including 12-O-tetradecanoylphorbol-13-acetate (TPA). Suppression of NK is mediated by monocytes or polymorphonuclear leukocytes (PMN) and suppression is dependent on the generation of reactive forms of molecular oxygen (RO), particularly hydrogen peroxide (H2O2). NK was suppressed not only by TPA but also by opsonized zymosan (yeast cell walls), which, like TPA, was not toxic to PBMC. Production of RO correlated with suppression of NK. Suppression could be restored by monocytes or PMN. Suppression of NK was dependent on RO. Suppression was also reduced in glucose-free medium, which did not support the generation of RO. Suppression of NK by TPA was inhibited by catalase. Bovine superoxide dismutase had a limited effect on suppression, and tyrosine-copper (II) complex, had almost no effect on suppression. When H2O2 was directly generated enzymatically from glucose oxidase and glucose, NK was suppressed and suppression was reversed by catalase. NK was also suppressed by the enzymatic generation of O2-from xanthine oxidase and xanthine, but suppression under these conditions was again inhibited by catalase and not by superoxide dismutase, indicating that suppression was due to the secondary formation of H2O2 from O2-. These results indicate that H2O2 is important in suppression of NK. Suppression of NK was reversible. These studies demonstrate cellular regulation of NK by monocytes or polymorphonuclear leukocytes and indicate a role for RO in immunoregulation. (68 Refs)

83. HYBRID RESISTANCE AGAINST A NATURAL KILLER (NK) CELL-RESISTANT LYMPHOMA (YWA) IS MEDIATED BY A T CELL-DEPENDENT MECHANISM.

Gronberg A, Klein GO, Karre K, Kiessling R, Klein G
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden
Eur J Cancer Clin Oncol; 18(2):183-190 1982

Rejection of the Moloney virus-induced YAC lymphoma of strain A origin by semisyngeneic F1 hybrids has previously been shown to correlate with the levels of natural killer (NK) cell activity in the same F1 hybrids against this target cell line in vitro. In the present study, YAC and another Moloney virus-induced lymphoma, YWA, derived from the A congenic A-SW strain, were tested for F1 hybrid resistance after sc inoculation of small numbers of cells into syngeneic and semisyngeneic F1 mice. While YAC cells invariably grew progressively once they formed a palpable tumor, regression of YWA tumors was frequently observed in both susceptible and resistant genotypes. The hybrid resistance pattern for YAC and YWA differed in one important respect: outcross of the syngeneic host to the A-congenic A-BY strain introduced a strong H-2b-associated resistance factor against YWA, but not against YAC. Compared to YAC, which is highly NK-sensitive and rapidly eliminated from mice with high NK activity, YWA was insensitive to NK-mediated lysis in vitro and [125I]UdR-labeled YWA cells were not eliminated more efficiently from the highly resistant (A-SW x A-BY) F1 than from the parental strain in short-term (4-18 hr) in vivo rejection assays. It was therefore concluded that the H-2b-associated resistance against YWA was independent of NK cells or other rapidly acting effector mechanisms. Moreover, thymectomy, followed by irradiation and fetal liver reconstitution, completely abolished the resistance against YWA but left the resistance against YAC virtually intact. These data suggest that two lymphomas induced by the same agent can be rejected by different effectors. The NK-resistant YWA lymphoma is rejected by a T-dependent mechanism, while the resistance against the inoculation of the highly NK-sensitive YAC line is T-independent and, in all probability, mediated by NK cells. (Author abstract) (22 Refs)

84. STUDIES ON THE MECHANISM OF NK CELL LYSIS.

Quan PC, Ishizaka T, Bloom BR
Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, Bronx, NY
J Immunol; 128(4):1786-1791 1982

The mechanism of cytolysis by murine NK cells was analyzed using a variety of metabolic inhibitors that have proven informative in studying the lytic mechanism of CTL and the mechanism of histamine release by mast cells. Target cell binding occurred in the absence of calcium and was inhibited by only one of the agents studied, cytochalasin B. Lysis was initiated by addition of Ca++ ions, as in the case of CTL. Subsequent to target cell binding, but prior to programming for lysis by Ca++, NK cell lytic activity could be suppressed by inhibitors of chymotrypsin-like, but not trypsin-like proteases, in contrast to CTL. In addition, 3-deaza-SIBA, an inhibitor of transmethylation reactions and quinacrine, an inhibitor of phospholipase A2, appear to act before the Ca++-dependent programming for lysis. Sr++ ions blocked the lytic function, as did trifluoperazine (stelazine), the former presumably competing for ionic calcium, the latter known to block binding of Ca++ to calmodulin. 8Br-cAMP and colchicine blocked later steps required for lysis. With the possible exception of trifluoperazine, all of the agents that blocked NK cell lysis are known to inhibit histamine release from mast cells. These results lend support to the stimulus-secretion model, originally proposed to explain the mechanism of CTL cytolysis, as relevant to the mechanism of lysis by NK cells. (Author abstract) (38 Refs)

85. TWO DISTINCT HUMAN CLONED T CELL LINES THAT EXHIBIT NATURAL KILLER-LIKE AND ANTI-HUMAN EFFECTOR ACTIVITIES.

Sugamura K, Tanaka Y, Hinuma Y
Inst. Virus Res., Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
J Immunol; 128(4):1749-1752 1982

Cloned T cell lines from mixed lymphocyte cultures stimulated with autologous Epstein Barr virus- (EBV) transformed lymphoblastoid cell line (LCL) cells were established using a limiting dilution technique in the presence of T cell growth factor (TCGF). The T cell lines included two distinct clones of cytotoxicity T cells (Tc) in addition to EBV-specific Tc. A cytotoxic profile of one cloned line was similar to that of endogenous NK cells in peripheral blood. The other cloned Tc line showed an anti-human cytotoxicity. The susceptible targets for this latter Tc line were various human cells, including autologous LCL and peripheral blood lymphocytes (PBL), stimulated with pokeweed mitogen, along with NK-sensitive and NK-resistant cell lines. Weak cytotoxic activity was detected against various xenogeneic cell lines. Furthermore, autologous and allogeneic cloned T cell lines were resistant to killing by the anti-human effector clone. These two distinct cloned Tc lines expressed the Leu-1 and Leu-2a antigens, which are markers of suppressor/cytotoxic T cells. (Author abstract) (23 Refs)

86. HUMAN TUMOUR ANTIGENS DEFINED BY CYTOTOXICITY AND PROLIFERATIVE RESPONSES OF CULTURED LYMPHOID CELLS.

Vose BM, Bonnard GD
Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD, 20205
Nature; 296(5855):359-361 1982

Methods of initiating continued lymphocyte cultures (CLC) having specific antitumor reactivity are described. Blood lymphocytes were obtained from cancer patients on the morning of surgery. The lymphocytes were grown in optimal quantities of different conditioned media containing interleukin-2 (IL-2) reactivity. The resulting cultured cells were tested for cytotoxicity against a range of target cells, including freshly isolated autologous and allogeneic tumor cells. The possible presence of natural killer (NK) cells was investigated with CLC against K562 cells. CLC showed cytotoxicity against both autologous and allogeneic tumor targets, and high levels of cytotoxicity against K562 cells were found in some conditioned media. No evidence of selective reactivity against the autologous tumor alone was found. Often, cytotoxicity against allogeneic tumors of unrelated types exceeded that against autologous tumors. Use of positive mixed lymphocyte-tumor cultures (MLTC) was critical to the experiments; cultures could be initiated from MLTC-negative individuals, but no specific reactivity was found in these CLC. Isolation of blast cells was necessary; without isolation, the cultured cells showed features of polyclonal T-cell activation and high NK activity. With the MLTC-CLC, selective lysis of autologous tumors and restimulation in primed lymphocyte test assays were demonstrated. (21 Refs)

87. TUMOR ENHANCING T LYMPHOCYTES IN MICE: FURTHER STUDIES ON CHARACTERISTICS AND MECHANISM OF ACTIVITY.

Small M
Dept. Histology and Cell Biology, Sackler Sch. Medicine, Tel-Aviv Univ., Ramat Aviv, Israel
Int J Cancer; 29(4):465-469 1982

In order to test the possibility that tumor-enhancing T lymphocytes can suppress other lymphoid cells, such as those with anti-tumor activity, their effect was tested in an allogeneic response of cell-mediated lysis. Normal thymocytes and spleen cells from mice with advanced tumors, two populations which enhance the growth of solid tumors, both suppressed the generation of CML. Since these results suggest that the mechanism of enhancement by T cells may resemble suppression in other immune responses, we looked for Fc receptors on the sensitized cells involved in tumor enhancement. Cells expressing Fc receptors appeared to be necessary for enhancement of tumor growth to occur. (Author abstract) (28 Refs)

88. CULTURED HUMAN T-CELL LINES KILL AUTOLOGOUS SOLID TUMOURS.

Vose BM, Moore M
Dept. Immunology, Paterson Laboratories, Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England
Immunol Lett; 3(4):237-241 1981

An investigation concerning the possibility that the cytolytic activity of autoreactive T-cells, present in various lymphocyte preparations from cancer patients, might be amplified by expansion of the relevant subpopulations in T-cell growth factor (TCGF; Interleukin 2), is presented. Lymphocytes from peripheral blood, lymph node, spleen and tumor of seven patients with various carcinomas (2 lung, 3 colon, 1 stomach) and a parotid tumor, were cultured for 15 days in conditioned media containing TCGF. Cytotoxic activity was then determined against autologous tumor (and some autologous normal) cells and allogeneic tumor targets as evaluated in a short-term 51Cr-release assay. Significant cytotoxicity was detected in at least one effector preparation from all patients. This result was obtained under conditions where, in some cases, other autologous cells (normal lung, phytohemagglutinin-transformed lymphocytes) were resistant. The cytotoxicity also generally extended to allogeneic tumor targets, but lysis of K562, a cell line sensitive to natural killing, occurred in only 3/19 effector cell preparations. The results represent the first demonstration of cytotoxicity in human cultured T-cells (CTC) directed against autologous solid human tumor cells. The data are consistent with a polyclonal expansion of CTC of tumor-bearing patients which includes the amplification of a population recognitive of antigens expressed on autologous neoplastic cells. (19 Refs)

89. T CELL REPLACING FACTORS IN THE B CELL RESPONSE TO ANTIGEN.

Swain SL, Wetzel GD, Soubiran P, Dutton RW
Dept. Biology, Univ. California, San Diego, La Jolla, CA, 92093
Immunol Rev; 63:111-128 1982

Experiments on the isolation and characterization of T cell replacing factor (TRF) from a long-term alloreactive T cell line, C.C3.11.75, are described. The activity found in this line was studied in an 'IL2 synergy' assay and given the provisional name (DL)TRF. B cells from certain lines did not respond to this TRF, which was not interleukin 1 or 2. This TRF can increase the frequency of induced B cell proliferation, act on a single B cell, and is necessary for immunoglobulin secretion in one model. (34 Refs)

90. MONOCLONAL ANTI-B CELL ANTIBODIES: THEIR EFFECTS ON HUMAN MIXED LYMPHOCYTE REACTIONS.

Steel CM, Van Heyningen V, Guy K, Cohen BB, Deane DL, Crichton D, Hutchins D
MRC Clinical and Population Cytogenetics Unit, Western General Hosp., Crewe Road, Edinburgh EH4 2XU, Scotland
Protides Biol Fluid Proc Colloq; 29:695-699 1982

The role in the mixed lymphocyte reaction (MLR) of antigens of three monoclonal anti-B-cell antibodies was defined with the micro-scale lymphocyte culture technique of Steel and Creasey. Studies included the isolated T cell response, effect of complement, antigen-negative stimulator, and lymphocyte stimulation by activated T cells. No clear pattern emerged from the studies on MLR inhibition by anti-B-cell monoclonals. Further analysis of the mechanisms involved in lymphocyte activation should be possible through the use of monoclonal reagents. (8 Refs)

91. HUMAN HELPER T CELL FACTOR(S) (THF). II. INDUCTION OF IGG PRODUCTION IN B LYMPHOBLASTOID CELL LINES AND IDENTIFICATION OF T CELL-REPLACING FACTOR-(TRF)LIKE FACTOR(S).

Teranishi T, Hirano T, Arima N, Onoue K
Dept. Immunobiochemistry, Kumamoto Univ. Sch. Medicine, 2-2-1, Honjo, Kumamoto 860, Japan
J Immunol; 128(4):1903-1908 1982

IgG-PFC was induced in Epstein-Barr virus-transformed B lymphoblastoid cell lines (LCL) by the addition of allogeneic T cells. T cells involved in the induction of IgG-PFC were shown to belong to the Leu 3a+/2a- T cell subset. Furthermore, partially purified soluble factors obtained from the culture supernatant of PPD-stimulated pleural T cells or PWM-stimulated tonsillar mononuclear cells was shown to induce IgG-PFC in LCL across the major histocompatibility complex barrier. The induction of IgG-PFC was observed only in surface IgG-positive LCL cell populations and was not accompanied by the increase in the number of LCL cells. The factors with such a TRF-like activity were found in two fractions corresponding to the mol wt range of 18,000 to 25,000 (22K fraction) and 28,000 to 38,000 (36K fraction) by gel filtration. Isoelectric focusing at these fractions revealed that TRF-like activity of both 22K and 36K fractions distributed in the pI range of 5.0 to 6.0, and both fractions were found to be devoid of TCGF activity. These results appear to indicate that the factors act on the B cells in terminal stages to trigger final differentiation to Ig-producing cells. (Author abstract) (35 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

92. CYANOGEN BROMIDE FRAGMENTS OF MOUSE IGG2A AND IGG2B WHICH BIND TO THEIR FC RECEPTORS ON MOUSE MACROPHAGES.

Diamond B, Campbell R, Schneck J, Birshtein BK
Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, 1300 Morris Park Ave., Bronx, NY, 10461
Protides Biol Fluid Proc Colloq; 29:415-418 1982

Identification of the portions of mouse IgG2b and IgG2a immunoglobulins recognized by their specific Fc receptors on mouse macrophages was determined with the use of cyanogen bromide fragments. A fragment from the Ch2 domain of IgG2b bound uniquely to the gamma2b Fc receptor while the gamma2a Fc receptor bound two widely spaced fragments, one from the CH2, and one from the CH3 domains. Fragments H-5 and H-10 competed with intact IgG2a protein for binding to the gamma2a Fc receptors. The binding of H-10 augments the binding of the H-5 fragment. The implications of these findings are discussed. (6 Refs)

93. THE RELEASE OF PLUTONIUM FROM MACROPHAGES IN RATS: THE EFFECTS OF CHANGES IN IRON STATUS.

Priest ND, Haines JW
Natl. Radiological Protection Board, Chilton, Didcot, Oxon OX11 ORQ, England
Health Phys; 42(4):415-423 1982

Female rats were used to study the loss of plutonium from hepatic and splenic macrophages. The plutonium was administered intravenously either as a 'soluble' [Pu] ferric hydroxide colloid or as an 'insoluble' plutonium dioxide suspension. The 'soluble' plutonium was lost much more rapidly from the liver than the 'insoluble' plutonium. If the iron status of the rats was altered, shortly after the injection of the [Pu] ferric hydroxide colloid, either by the removal of blood or by the injection of colloidal iron, the rate of plutonium loss from the liver was changed. The plutonium was retained longer in those animals with excess storage iron than in those with depleted circulatory iron. These results are taken to indicate that iron and plutonium share common pathways of metabolism in macrophages. (Author abstract) (21 Refs)

94. THE MACROPHAGE AS A CYTOTOXIC EFFECTOR CELL.

Lohmann-Matthes ML
Max-Planck-Institut fur Immunobiologie, Stubeweg 51, 7800 Freiburg, W. Germany
Haematol Blood Transfus; 27:49-57 1981

Macrophages possess three different mechanisms to act as cytotoxic effector cells: lymphokine-induced macrophage cytotoxicity shows a clear preference for tumor targets; young macrophages and macrophage precursor cells kill antibody coated nucleated target cells; and nonadherent, nonphagocytic macrophage precursor cells show strong natural killer activity. Different subpopulations appear to be responsible for the various macrophage functions. The three mechanisms enhance and cooperate with each other and are probably important in the cytotoxic defense system of the body. (33 Refs)

95. HUMAN PULMONARY MACROPHAGES. PINOCYTIC ACTIVITY IN BRONCHIAL CARCINOMA AND IN THE PRESENCE OF LEVAMISOLE AND CYCLOSPORIN A.

Plowman PN
Dept. Radiotherapy, St. Bartholomew's Hosp., West Smithfield, London EC1, England
Clin Oncol; 8(1):39-48 1982

Human pulmonary macrophages have been obtained by bronchopulmonary lavage from lung segments adjacent to a bronchial carcinoma and from normal lungs. Using fixed volume lavages, the lavage effluent from smokers contained more cells and a higher proportion of macrophages than the effluent from non-smokers. Amongst non-smokers, the lymphocyte-macrophage ratio in the lavage effluent was unchanged in the presence of primary bronchial carcinoma. The pinocytic activities of pulmonary macrophages from cancer bearing lungs were compared to those from normal lungs. There was a wide range of pinocytic activities demonstrated in the cancer group but a significant skew towards the lower pinocytic activities was seen; this could be distinguished from the effect of smoking which appeared to increase pinocytic activities. Neither levamisole (10(-5) -10(-3) M) nor cyclosporin A (5-50 ug/ml) modified the intrinsic pinocytic activities of human pulmonary macrophages in this in vitro assay. (Author abstract) (17 Refs)

96. THE REGULATION OF BONE MARROW-DERIVED MONONUCLEAR PHAGOCYTE DIFFERENTIATION AND MOBILIZATION IN SYNGENEIC AND ALLOGENEIC YAC-LYMPHOMA-BEARING MICE.

Bursuker I, Goldman R
(c/o Goldman) Dept. Membrane Res., Weizmann Inst. Science, Rehovot, Israel
Cell Tissue Kinet; 15(2):145-156 1982

YAC-lymphoma inoculation (ip) into syngeneic A/J mice results in a massive in situ proliferation of the lymphoma cells, with non-significant increases in the peritoneal macrophage population, and also in a remarkable and progressive increase in the bone marrow precursor cells forming both macrophage and fibroblastoid colonies in vitro. In the allogeneic situation (BALB/c mice), YAC-lymphoma cells proliferate to a limited extent before tumor regression. These processes (ie proliferation and regression) were accompanied by a progressive increase in the peritoneal macrophage population, which declined to normal after tumor regression. Macrophages accumulating at the regression stage exhibited in vitro cytolytic activity towards YAC-lymphoma cells and cytostatic activity towards unrelated cells. No correlation was observed between the limited asynchronous increase in the bone marrow level of precursor cells for in vitro differentiating macrophage and fibroblastoid colonies, on one hand, and macrophage accumulation at the tumor site in BALB/c mice on the other. Conditioned media from in vitro proliferating YAC-lymphoma cells exhibited high colony-stimulating activity for macrophage colony formation in vitro. Bone marrow cells taken from YAC-lymphoma inoculated A/J mice expressed potent tumorigenic potential at early stages after tumor inoculation. At Day 2 after tumor inoculation the bone marrow cells were already tumorigenic and concomitantly expressed augmented levels of macrophage and fibroblastoid colony-forming capacity. The results indicate an inter-relationship between tumor growth and mononuclear phagocyte differentiation and proliferation. (Author abstract) (30 Refs)

97. CHARACTERIZATION OF A MACROPHAGE CHEMOKINETIC FACTOR IN TUMOR CELL CULTURE MEDIA.

Lane RD, Kaplan AM, Sondgrass MJ, Szakal AK
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J Reticuloendothel Soc; 31(2):171-184 1982

Media conditioned by tumor cells were studied for the presence of factor(s) that increase the rate of random migration (chemokinesis) of Corynebacterium parvum-activated macrophages. A capillary tube assay was developed and utilized to expediently monitor the chemokinetic activity of macrophages incubated in whole and fractionated media. Media conditioned by six different syngeneic and allogeneic mouse tumor cell lines demonstrated significantly higher chemokinetic activity than unconditioned or normal fibroblast conditioned media. The chemokinetically active component of the Lewis Lung conditioned media was found to be a trypsin sensitive, heat stable, high molecular weight (300,000-480,000 dalton range) factor that had no chemotactic (directional migration) activity. Pyran-activated macrophages also responded chemokinetically to the Lewis Lung factor while oyster glycogen and thioglycolate-elicited macrophages did not. The similarity and differences between the physical properties of the chemokinetic factor, other migration stimulating factors, and tumor-associated proteins are discussed. (Author abstract) (30 Refs)

98. INHIBITION OF CELLULAR DIVISION OF A MURINE MACROPHAGE TUMOR BY MACROPHAGE-ACTIVATING AGENTS.

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Cancer Metastasis and Treatment Lab., NCI-Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 42(5):1850-1855 1982

Although the murine reticulum cell sarcoma M5076 is highly malignant in vivo, in vitro it displays many of the functional characteristics of an activated macrophage, such as phagocytosis and tumor cytotoxicity. This study was designed to determine what effect macrophage-activating agents would have on the function and growth of M5076 cells. Exposure of M5076 tumor cells to substances that activate normal macrophages to the tumoricidal state rapidly and irreversibly induced cessation of cellular division. The treated tumor cells, however, retained the same characteristics as those of untreated M5076 cells in vitro with respect to viability and the activated macrophage functions of phagocytosis and tumor cytotoxicity. Even after a short exposure to lipopolysaccharide, the ability of M5076 cells, injected iv into syngeneic mice, to form tumor nodules was greatly reduced. These results indicate that a highly malignant tumor of macrophage origin, M5076, can be induced to cease cellular division while retaining the functional attributes of an activated macrophage. We speculate that the exposure of M5076 to macrophage-activating agents results in the induction of terminal differentiation of this tumor. (Author abstract) (30 Refs)

99. SERUM MIGRATION INHIBITORY ACTIVITY AGAINST MACROPHAGES AND TUMOR CELLS.

D'Silva H, Cohen M, Yoshida T, Cohen S
Dept. Pathology, Univ. Connecticut Health Center, Farmington, CT, 06032
Clin Immunol Immunopathol; 23(1):77-85 1982

A factor that can inhibit the migration of tumor cells without cytotoxic effect (TMIF) is present in supernatants of activated lymphocytes. In the present experiments, we demonstrate that similar activity can be found in the serum of appropriately immunized animals. As is the case for macrophage migration inhibitory factor (MIF), TMIF activity appears only transiently after challenge with antigen. TMIF is also found in the serum of tumor-bearing animals. In this situation, activity persists from Day 7 postinoculation until the time of death. Although previous studies have demonstrated that TMIF and MIF are distinct, these results show that TMIF activity parallels serum migration inhibitory activity against macrophages. In the present experiments, the animals were given a lethal dose of tumor cells. However, it is likely that by virtue of its biologic properties, TMIF might have a protective effect under other experimental conditions. (Author abstract) (8 Refs)

100. TUMOUR-PROMOTING DITERPENE ESTERS PREVENT MACROPHAGE ACTIVATION.

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Br J Cancer; 45(1):144-146 1982

Peritoneal wash-outs from normal DA rats or C3H/J mice were interacted for 8 hr with macrophage-activating lymphokines. 14C-Deoxythymidine-labeled DA rat polyoma-induced tumor cells were interacted with effector cells for 36 hr at 37 C; the released radioactivity was measured and net cytotoxicity calculated. The phorbol esters 12-O-tetradecanoyl-phorbol-13-acetate (TPA), phorbol-12,13-didecanoate (PDD), and the 1alpha-alkyldaphnane, Pimelea factor P2, were similarly active in preventing lymphokine-induced or spontaneous enhancement of macrophage tumoricidal activity. Manifestation of macrophage cytotoxicity was inhibited whether or not effector cells were first pretreated for 4 hr with tumor promoters and the washed effector cells interacted with prelabeled targets, or the promoting agents were present throughout the entire 36-hr effector/target cell interaction. Thus, active tumor promoters of the phorbol diester- and daphnane-type prevent lymphokine-induced enhancement of macrophage cytolysis; such a capacity to suppress activation or manifestation of cytotoxicity by rat and mouse macrophages may be common to all tumor promoters. Tumor promoters may facilitate the outgrowth of transformed cells by stimulation of their multiplication and functional capacities and by suppression of the host's cellular antitumor effector systems. (11 Refs)

101. RELATIONSHIP OF CELL-CYCLE EXPRESSION OF IA-LIKE ANTIGENIC DETERMINANTS ON NORMAL AND LEUKEMIA HUMAN GRANULOCYTE-MACROPHAGE PROGENITOR CELLS TO REGULATION IN VITRO BY ACIDIC ISOFERRITINS.

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J Clin Invest; 69(3):632-642 1982

An association has been established between human Ia-like (Ia) antigenic determinants, expression during DNA synthesis on granulocyte-macrophage colony forming cells (CFU-GM) and the regulatory action of acidic isoferritins in vitro. Treatment of human bone marrow cells with monoclonal-anti-Ia-like (Ia) plus complement inhibited colony and cluster formation by approx 50% but did not affect pre-CFU-GM. Reduction of colonies and clusters was similar whether bone marrow cells were exposed to anti-Ia plus complement, high specific activity tritiated thymidine (3HTdr) or acidic isoferritins. No further decrease was apparent with 3HTdr or acidic isoferritins after Ia-antigen+ CFU-GM were removed, or with anti-Ia plus complement or acidic isoferritins after DNA synthetic phase (S-phase) CFU-GM were removed. Anti-Ia, without complement, did not reduce colony or cluster formation but did block the inhibitory action of acidic isoferritins. A relationship existed between Ia antigens and the activity of acidic isoferritins in the following ways: (a) The apparent loss of Ia-antigens from CFU-GM by 5 hr in culture at 37 C, but not at 27 C or 4 C, was associated with nonresponsiveness to inhibition with acidic isoferritins, (b) Ia-antigen-, noncycling pre-CFU-GM that were insensitive to acidic isoferritins could generate a population of Ia-antigen+ cycling CFU-GM in vitro that were responsive to inhibition by acidic isoferritins, and (c) nondetectability of Ia-antigens on CFU-GM from patients with leukemia was associated with nonresponsiveness to inhibition by acidic isoferritins. These results implicate Ia-antigen+ progenitor cells in the regulation of myelopoiesis in vitro and demonstrate that absence of Ia-antigens on patient CFU-GM is associated with imbalances in normal regulatory interactions in vitro. These findings may be of relevance to normal regulation and to the progression of leukemia. (Author abstract) (30 Refs)

102. THE EFFECT OF PROTEIN DEPLETION ON BONE MARROW MYELOID CELL REPOPULATION.

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J Surg Res; 32(3):264-268 1982

We studied the effect of protein depletion on bone marrow recovery after injection of the cytotoxic drug, 5-fluorouracil (5-FU), by using an in vitro quantitative clonal culture technique for femoral marrow granulocyte/macrophage progenitor cells (GM-CFC). Mice were maintained for 7 days on either a regular diet or on a protein-free but isocaloric and otherwise complete diet. Groups of animals were assayed 1-5 and 7 days after 40 mg/kg ip 5-FU. Both regular-diet animals and animals on the protein-free diet had similar GM-CFC toxicity 1 day after 5-FU injection. However, 5 days after 5-FU, protein-depleted animals were significantly different from regular diet animals in the extent of repopulation of the GM-CFC (confidence 95%). Regular diet animals demonstrated a rebound overshoot of the progenitor cells which was not found in protein-depleted animals. The extent of recovery of the GM-CFC at 7 days after 5-FU for the protein-depleted animals still did not equal that of the regular diet animals (90% confidence). Quadratic regression analysis of the recovery curves for both regular diet and protein-free diet animals for days 1-7 following 5-FU were significantly different (p less than 0.01). We conclude that while protein depletion does not alter the acute bone marrow toxicity of 5-FU, protein-depleted animals had an impaired rate and extent of repopulation of the myeloid progenitor cells. These findings may form the basis for a clinical policy of dietary repletion in selected malnourished cancer patients prior to chemotherapeutic treatment. (Author abstract) (22 Refs)

103. CHANGES IN PROSTAGLANDIN LEVELS IN CULTURES OF SV40-TRANSFORMED MACROPHAGE CELL LINES IN RELATION TO THEIR PHENOTYPIC EXPRESSION.

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Microbiol Immunol; 26(1):59-66 1982

Prostaglandin (PRG) levels were determined in culture fluids of simian virus 40-transformed cells, line 28-12 and its subline, and the release of PRG by the cells when they are treated with lipopolysaccharide (LPS) and OK-432 (a streptococcal preparation from penicillin-attenuated Streptococcus pyogenes) was investigated. Low levels of PRG were detected in Dulbecco's modified Eagle's medium, and significantly higher levels (4,921 +-140 picog/ml) were detected in heat-inactivated fetal calf serum. 28-12 cells were cultivated for 16 days and the medium was changed every 4 days. A low level of PRG was detected in 4-day culture medium during the growing phase of the cells. When the proportion of phagocytic cells increased during the stationary phase, a decrease in PRG levels was observed. The levels of PRG remained lower than background levels and constant during the culture period when the 28-12 subline isolated by cultivation with cytosine arabinoside (28-12Ara) was cultivated without a change in the medium for 4 days. Non-phagocytic 28-12 cells and phagocytic 28-12Ara cells were cultivated for 24 hr in the presence and absence of LPS (1 ug/ml) and OK-432 (25 ug/ml). The release of PRG by 28-12Ara cells was markedly enhanced, whereas its release by 28-12 cells was not affected. The results indicate the correlation between the phenotypic change from the nonphagocytic to the phagocytic state and a decrease in PRG levels in culture fluids, and that phagocytic cells are responsive to PRG inducers, whereas nonphagocytic cells are not. (27 Refs)

104. A PHORBOL ESTER (TPA) CAN REPLACE MACROPHAGES IN HUMAN LYMPHOCYTE CULTURES STIMULATED WITH A MITOGEN BUT NOT WITH AN ANTIGEN.

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J Immunol; 128(4):1776-1780 1982

A culture system was developed in which human peripheral blood mononuclear cells (PBM) depleted of macrophages did not proliferate in response to the lectin mitogen PHA or to the soluble antigen of tetanus toxoid. These cells were able to respond to both mitogen and antigen if purified autologous macrophages were added back to the culture. The response to PHA was partially restored by supplementing the cultures with supernatants from LPS-stimulated macrophages or with partially purified human interleukin 1 (IL 1). The response to tetanus was not restored by reconstitution with these materials. The phorbol ester, 12-O-tetradecanoyl-phorbol-13-acetate (TPA), has been shown to have IL 1-like effects in other species and is a polyclonal activator of human T and B lymphocytes. In this study, we tested the ability of TPA to replace macrophages in human lymphocyte cultures stimulated with mitogen or with antigen. Small doses of TPA (50 ng/ml) completely replaced macrophages in the PHA-stimulated cultures; however, in doses of up to 400 ng/ml, TPA was not able to replace macrophages in cultures stimulated with tetanus. Thus, TPA appears to mimic the macrophage-replacing ability of soluble factors (IL 1, macrophage supernatants) in the triggering of human lymphocytes. (Author abstract) (31 Refs)

105. THE RELATIONSHIP BETWEEN COMPETENCE FOR SECRETION OF H2O2 AND COMPLETION OF TUMOR CYTOTOXICITY BY BCG-ELICITED MURINE MACROPHAGES.

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J Immunol; 128(4):1781-1785 1982

BCG-elicited macrophages from C3H/HeJ and A/J mice secrete H2O2 comparably to BCG-elicited macrophages from control C3H/FeJ mice in response to the pharmacologic stimulant phorbol myristate acetate. By contrast, BCG-elicited macrophages from C3H/HeJ and A/J mice could not effect tumor cytotoxicity, whereas macrophages from the control C3H/FeJ mice could. When BCG-activated macrophages from C57BL/6J mice were held in culture overnight, their ability to secrete H2O2 in response to the pharmacologic trigger declined 40 to 60%; the presence of endotoxin in the overnight cultures did not alter competence for secretion of H2O2. By contrast, the cultured macrophages lost all of their cytolytic competence, but this competence could be fully maintained by the presence of endotoxin in the cultures. In three distinct circumstances, competence for secretion of H2O2 thus did not correlate with competence for completion of tumor cytotoxicity. The data imply that competence for release of H2O2 is not sufficient for completion of tumor cytotoxicity. (Author abstract) (37 Refs)

106. EFFECT OF MACROPHAGES ON PHORBOL ESTER STIMULATED COMITOGENESIS IN BOVINE LYMPHOCYTES.

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Cancer Res; 42(5):1630-1635 1982

12-O-Tetradecanoylphorbol-13-acetate (TPA) added together with mitogenic lectins to bovine lymph node lymphocytes causes a synergistic increase in DNA synthesis. This comitogen effect is due to an increase in cell proliferation. To determine the role of macrophages in comitogenesis, lymphocyte preparations were depleted of macrophages by sequential adherence to glass, plastic, and nylon wool. Phagocytic cells were removed by incubation with carbonyl iron and a magnet. After macrophage depletion, the lymphocyte response to lectins decreased, indicating the accessory function of macrophages in mitogenesis. The addition of TPA or macrophages to the depleted cultures restored its response to that of the unfractionated cells. TPA was still comitogenic with lectin in lymphocyte preparations from which all residual macrophages were removed by antimacrophage serum and complement. Therefore, the comitogenic effect of TPA is independent of macrophages in these cultures. (Author abstract) (38 Refs)

107. EFFECT OF FEEDER LAYER ACTIVITY ON BUOYANT DENSITY DISTRIBUTIONS OF GRANULOCYTE-MACROPHAGE COLONY FORMING CELLS.

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Scand J Haematol; 28(1):39-44 1982

Separation of bone marrow cells in continuous bovine serum albumin density gradients and the agar culture technique were used to determine the buoyant density distribution of granulocyte-macrophage colony forming cells (CFUc) from normal marrow. The results showed that the buoyant density distribution of normal CFUc is dependent on the activity of the feeder layers used to stimulate colony formation and the additional low density CFUc grow on high activity feeder layers. The implications of these findings for studies of the density of acute myeloid leukemia CFUc will be discussed. (Author abstract) (8 Refs)

108. PERITONEAL CELL POPULATIONS DURING TUMOR INJECTION: QUANTITATIVE CHANGES IN NUMBERS OF PERITONEAL MONONUCLEAR PHAGOCYTES AND CHANGES IN THE BETA-GLUCURONIDASE ACTIVITY OF THESE CELLS IN NORMAL AND IN (SYNGENEIC AND ALLOGENEIC) IMMUNIZED MICE AFTER INTRAPERITONEAL INJECTION OF TUMOUR CELLS.

De Heer E, De Groot JW, Den Otter W, Dullens HF
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Int J Tissue React; 4(1):81-90 1982

To elucidate the cellular (immune) events leading to tumor rejection, the characteristics of the peritoneal cell population kinetics were studied following ip injection of normal, irradiated, or mitomycin C-treated SL2 lymphosarcoma cells in allogeneic C57BL and syngeneic DBA/2 mice. The mice were first primed ip with tumor cells according to four different immunization schedules. Injection of tumor cells caused a dose-dependent increase in the number of host peritoneal cells (neutrophils, macrophages, and lymphocytes) in both the allogeneic and syngeneic systems. With low doses of tumor cells, the peak in the number of cells was lower as well as later in time. With immunized mice, injection of tumor cells produced a temporary macrophage disappearance reaction in both the syngeneic and allogeneic systems, which was not dependent on the dose. This depletion may represent an in vivo manifestation of delayed-type hypersensitivity. In both the syngeneic and allogeneic systems, no quantitative differences in the cellular response to either untreated, mitomycin C-treated or irradiated cells were noted. Qualitatively, immunization with irradiated tumor cells resulted in a stronger antitumor efficacy of the peritoneal cells than after immunization with mitomycin C-treated cells. The lysosomal activity of peritoneal macrophages, measured as beta-glucuronidase activity, was influenced by dose, with higher doses of SL2 cells inducing a long-lasting enzyme activity. The increase may represent a cytotoxic response of the macrophages. Thus, the cellular events leading to tumor cell rejection depend upon the initial antigenic challenge, with rejection influenced by quantitative as well as qualitative differences in the peritoneal cell population. (20 Refs)

109. SUPPRESSIVE EFFECT OF ADHERENT MONONUCLEAR CELLS FROM PERIPHERAL BLOOD OF PATIENTS WITH HODGKIN'S DISEASE ON PHA RESPONSIVENESS.

Moghe MV, Advani SH, Gangal SG
Immunology Div., Cancer Res. Inst., Tata Memorial Centre, Bombay 400 012, India
Indian J Exp Biol; 19(12):1101-1106 1981

The possible suppressive effect of adherent cells from peripheral blood mononuclear cells (PBMNC) of patients with Hodgkin's disease (HD) on phytohemagglutinin (PHA) responsiveness of lymphocytes from healthy donors was investigated using allogeneic co-cultures. PBMNC were obtained from 22 untreated HD patients. Depletion of adherent cells from HD PBMNC resulted in three different responses: decreased PHA response compared with that of normal donors (27%), increased PHA responsiveness (27%) indicating monocyte-induced suppression, and no change in PHA responsiveness (45%) suggesting that suppressor cells could exist in the nonadherent population. Adherent cells from all categories caused depression in mitogen responsiveness of normal lymphocytes. Following depletion of autochthonous adherent cells, the addition of normal adherent cells appeared to augment the mitogen response in 75% of HD patients. These results demonstrate that the mitogen response of HD lymphocytes may be influenced by the balance between subpopulations of monocytes rendering suppression and help in addition to suppressor lymphocytes. In 69% of tests with normal adherent cells, the monocytic help provided to HD lymphocytes was abrogated by the addition of carageenan; with HD adherent cells, such an effect was observed in only 47% of tests. Thus, under the experimental conditions used, normal monocytes were inactivated to a greater extent than HD monocytes by the same dose of carageenan. HD monocytes may have different phagocytic activity and lysosomal differentiation required for activity of carageenan. (26 Refs)

110. LYSOSOMAL GRANULES IN LEUKEMIC MONOCYTES AND THEIR RELATION TO MATURATION STAGES.

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MRC Pathology, Hammersmith Hosp., Royal Postgraduate Medical Sch., Ducane Road, London W12 OHS, England
Haematol Blood Transfus; 27:167-173 1981

Bone marrow and/or peripheral blood cells from 11 patients with monocytic leukemia were studied with light and transmission electron microscopy (TEM) cytochemical techniques. Two of the patients had monoblastic transformation of chronic granulocytic leukemia. Seven patients had poorly differentiated and four had differentiated leukemia. Cytochemical reactions for myeloperoxidase (MPO), Sudan Black B, acid phosphatase (AP), naphthol-AS acetate esterase, and alpha naphthyl acetate esterase were performed. TEM was used to examine cell morphology and for evaluation and localization of MPO and AP activity. Conventional TEM in two cases revealed typical ribosome-lamella complexes. AP and MPO reactions at the TEM level revealed three types of lysosomal granules: primary granules were the smallest in size, were mainly seen in monoblasts and were characteristically AP positive; secondary granules were seen from the promonocyte stage onwards, were of medium size, were MPO positive with some AP activity, and persisted, but in smaller numbers, with maturation; tertiary granules were of variable size and were negative for AP and MPO. These results demonstrated the sequential development of lysosomal enzymes during monocytic differentiation. (7 Refs)

111. THE KINETICS OF MONONUCLEAR PHAGOCYTES IN MAN.

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Haematol Blood Transfus; 27:11-22 1981

Essential steps of a systematic cell kinetic analysis of monocytopoiesis (MCP) in human bone marrow and blood monocytes are summarized. Normal conditions of mononuclear phagocytes (MNP) in bone marrow, stem cell to blood transit time of MCP, DNA synthesis time and cell cycle time of MNP in marrow, cell egress from precursor compartments into the blood are presented. A model for normal human MCP, blood monocyte and macrophage kinetics are discussed. Increased monocyte production, regulation of MCP, and MCP in disease states are reviewed. (30 Refs)

112. ACUTE AND PROGRESSIVE LUNG INJURY AFTER CONTACT WITH PHORBOL MYRISTATE ACETATE.

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Am J Pathol; 107(1):29-35 1982

Because of its potent ability to activate leukocytes and macrophages, resulting in the generation of large amounts of oxygen products (O(-)2, H2O2), phorbol myristate acetate (PMA) has been instilled into the airways of rats. The resulting acute lung injury is dose-dependent on the amount of PMA employed, is chiefly confined anatomically to the alveolar and interstitial compartments, is neutrophil-dependent, and can be inhibited by catalase but not by superoxide dismutase. These data suggest that the generation of H2O2 is a major mechanism involved in this model of acute lung injury. It has also been demonstrated that a progressive pattern of lung injury develops after exposure to PMA, with the onset of an interstitial fibrotic reaction by the 6th day. These data reinforce our recent studies, in which both acute and progressive injury occurs in lungs of rats when H2O2 is generated. (Author abstract) (12 Refs)

113. PEANUT AGGLUTININ: A NEW MARKER FOR TISSUE HISTIOCYTES.

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Am J Clin Pathol; 77(4):401-408 1982

The histiocyte (macrophage) is a unique cellular constituent of the immune system which is involved in immune and non-immune cellular reactions as well as in the genesis of a variety of benign and malignant neoplasms. The ability to distinguish histiocytes from similar appearing cells morphologically, is often difficult, yet may be of considerable practical and theoretical importance. The present study describes a new marker for histiocytes, applicable to routinely processed tissues. An immunoperoxidase procedure to detect binding of peanut agglutinin (PNA) was applied to 58 specimens consisting of lymph nodes, extranodal lymphoid tissues, neoplasms and reactive histiocytic lesions. Results were compared with a currently accepted histiocytic marker - cytoplasmic muramidase. Of the 58 tissues, 51 showed PNA binding to morphologically recognizable histiocytes, whereas muramidase was detected in only 44. PNA binding, appeared at least as sensitive and specific as muramidase, as a marker for histiocytes, and offers the advantage that it does not bind to cells of the granulocytic series. (Author abstract) (18 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

114. ENHANCEMENT OF HUMAN B LYMPHOCYTE DIFFERENTIATION IN VITRO BY THYROID HORMONE.

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Scand J Immunol; 15(2):211-215 1982

A study was made of the regulatory influence of a thyroid hormone, triiodothyronine (T3), on human blood T- and B-lymphocyte responses in vitro. Blood lymphocytes were stimulated with the T-cell mitogens concanavalin A (Con A) and phytohemagglutinin (PHA), with the T-dependent B-cell activator pokeweed mitogen (PWM), and with the T-independent B-cell activator Staphylococcus aureus Cowan I bacteria in the presence of various hormone concentrations. T3 did not stimulate T-cell proliferation. The number of immunoglobulin-containing and -secreting cells (plasmablasts) was increased in PWM and Staph aureus cultures treated with T3. The maximal enhancement was reached at a concentration of 10(-9) -10(-7) M T3. Cell fractionation techniques revealed that T3 apparently had a direct stimulatory effect on B-cell differentiation. (Author abstract) (18 Refs)

115. PRELIMINARY STUDIES ON ESTIMATION AND APPLICATION OF LYMPHOCYTE ALPHA-NAPHTHYL ACETATE ESTERASE.

Sun G, Liao Y, Zhu X, Zhou S, Xue Z, Li G, Dai Y, Hu Y, Zheng S
Dept. Biochemistry, Pediatric Inst., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Zhonghua Yixue Jianyan Zazhi; 4(2):76-78 1981

Alpha-naphthyl acetate esterase (ANAE) activity is generally considered a characteristic of T-lymphocytes. This study was undertaken to evaluate the conditions for the ANAE assay, factors that influence its accuracy and the relationship between ANAE activity and T-lymphocytes. Results indicated that although most T-lymphocytes had ANAE activity, this activity was not unique to the T-cells, especially in pathological conditions such as leukemia. Furthermore, substrate concentration, pH and reaction time also influenced the assay results. (4 Refs) (In CHI)

116. MONOCLONAL ANTIBODIES AGAINST HUMAN THYMOCYTES AND T LYMPHOCYTES.

Tax WJ, Willems HW, Kibbelaar MD, De Groot J, Capel PJ, De Waal RM, Reekers P, Koene RA
Dept. Nephrology, St. Rabdoudziekenhuis, Nijmegen, The Netherlands
Protides Biol Fluid Proc Colloq; 29:701-704 1982

The specificity of two cytotoxic monoclonal antibodies (WT 1 and WT 2) produced by the hybridoma technique was analyzed by cytotoxicity, indirect immunofluorescence, and the enzyme-linked immunosorbent assay. WT 1 was reactive with all human thymocytes and all peripheral T lymphocytes, but did not react with any other cell type from peripheral blood. WT 1 also bound to phytohemagglutinin (PHA)-stimulated T cells and to cytotoxic T lymphocytes induced by mixed lymphocyte culture. Monkey lymphocytes also reacted with WT 1 and therefore functional aspects of this antibody, such as immunosuppressive activity, can be studied in the monkey. WT 1 was not mitogenic and did not interfere with PHA stimulation. WT 1 did not block formation of erythrocyte-rosettes and appeared to be unreactive with myeloid progenitor cells. On the other hand, the growth of myeloid colonies was inhibited by prior incubation of bone marrow cells with rabbit complement and monoclonal antibody WT 2. WT 2 was not reactive with peripheral granulocytes or monocytes, and bound to all thymocytes and a small percentage of peripheral lymphocytes. (10 Refs)

117. LONG-TERM HUMAN CYTOLYTIC T-CELL LINES ALLOSPECIFIC FOR HLA-DR6 ANTIGEN ARE OKT4+.

Krensky AM, Reiss CS, Mier JW, Strominger JL, Burakoff SJ
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Proc Natl Acad Sci USA; 79(7):2365-2369 1982

Human allospecific cytotoxic T lymphocyte lines were established by weekly stimulation of peripheral blood lymphocytes with allogeneic Epstein-Barr virus-transformed lymphoblastoid cell lines in the presence of interleukin 2. The cytotoxic T lymphocyte lines were stimulated by either JY (which expresses HLA-A,B and -DR) or Daudi (which expresses HLA-DR but not -A,B antigens). Specificity of the effector cell lines was determined by antibody blocking and by patterns of cytolysis against a panel of target cell lines. The phenotype of the effector cells was identified by both negative (antibody and complement lysis) and positive (fluorescence-activated cell sorter) selection. The anti-JY lines only recognized targets bearing HLA-A2 or B7 antigens and were composed exclusively of OKT4-8+ effector cells. The anti-Daudi lines, on the other hand, specifically recognized targets bearing DR6 and eventually contained only OKT4+8-cells. Thus, stimulation by Daudi cells can result in the generation of OKT4+ CTL lines that are allospecific for DR6 antigen. (Author abstract) (34 Refs)

118. SPECIFICITY STUDIES OF CYTOLYTIC T LYMPHOCYTES DIRECTED AGAINST MURINE LEUKEMIA VIRUS-INDUCED TUMORS. ANALYSIS BY MONOCLONAL CYTOLYTIC T LYMPHOCYTES.

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J Exp Med; 155(4):1050-1062 1982

Specificities of cloned cytolytic T lymphocytes (CTL) were investigated for the analysis of CTL populations generated against murine leukemia viruses (MuLV) in H-2 congenic BALB/c (H-2d) and BALB.B (H-2b) mice. CTL elicited by immunization with syngeneic Friend or Gross MuLV-induced tumors in these mice were studied. Optimal conditions for proliferation and long-term culture of MuLV-specific CTL were determined. Ninety-two lymphocyte clones were assayed independently on a panel of 51Cr-labeled tumor target cells. Clones were then distributed into different groups according to their specificities. Most of the CTL clones (52-64%) attacked the tumor cell against which they were initially primed and not any of the other tumor cells assayed. Other clones were specific for the priming MuLV-induced antigen in apparent association with an H-2 public specificity shared between H-2b and H-2d antigens (5-16%); were specific for tumor cells induced by Gross, Rauscher, Friend, and Moloney MuLV and were H-2 restricted (6 clones); was H-2b restricted and recognized only RBL-5 and HFL/b tumor cells of the Friend, Moloney, or Rauscher family (1 clone); showed a total lack of target specificity (21 clones); or lacked detectable cytotoxic activity (2 clones). Thus, the highly heterogeneous constitution of CTL populations generated against MuLV-induced tumors in BALB/c and BALB.B mice was demonstrated. (40 Refs)

119. STUDIES OF THE PROPERTIES OF A STREPTOCOCCAL PREPARATION OK-432 (NSC-B116209) AS AN IMMUNOPOTENTIATOR. II. MECHANISM OF MACROPHAGE ACTIVATION BY OK-432.

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Cancer Immunol Immunother; 12(2):141-146 1982

The ability of the streptococcal preparation OK-432 to induce the cytotoxic activity of plastic-adherent mouse peritoneal exudate cells (PEC) through activation of the third component (C3) of complement was examined. C3 binding to OK-432 increased linearly with increasing OK-432 concentrations. When EDTA was used to prevent C3 activation, little binding was observed. Radiolabelling and immunofluorescence studies indicated that C3-OK-432 complexes bind to PEC through the C3 receptors. PEC pretreated with C3-OK-432 markedly reduced the uptake of 3H-thymidine by MM2 mouse mammary tumor cells in the presence of resident PEC. PEC pretreated with OK-432 did not cause such a marked reduction of the uptake suggesting that C3-OK-432 complexes trigger cytostatic activity of resident PEC through binding of complexes to the C3 receptor sites of the PEC. PEC from mice pretreated with OK-432 showed cytostatic activity and MM2 tumor growth inhibition. The mechanism of PEC (presumably macrophages) activation by OK-432 is discussed. (23 Refs)

120. MACROPHAGES IN HUMAN TUMOURS: AN IMMUNOHISTOCHEMICAL STUDY.

Nash JR
Nuffield Dept. Pathology, Univ. Oxford, John Radcliffe Hosp., Oxford, England
J Pathol; 136(2):73-83 1982

Human gastrointestinal, breast, and other tumors were stained for acid phosphatase (AP), non-specific esterase (NSE), and lysozyme to assess the usefulness and specificity of the methods in assessing tumor macrophage content. Of the 48 tumors studied by lysozyme staining, 22 were studied with NSE staining and 9/22 were further studied by AP staining. All colonic tumors contained few lysozyme-positive macrophages (LPM) within the tumor, an amount similar to the surrounding non-malignant mucosa. Most colonic tumors showed LPM concentrated around the tumor edge; this was less apparent in tumors from more proximal parts of the gastrointestinal tract. Negligible macrophage infiltration was found in 13//15 breast carcinomas. Other tumors showed negligible numbers of macrophages, with the exception of a metastatic squamous carcinoma deposit in a lymph node and a transitional cell carcinoma of the bladder. Normal and inflamed tissues contained variable numbers of macrophages, and lysozyme staining was often very faint in epithelioid and giant cells. AP and NSE staining was more difficult to assess because there often was no way to discriminate between tumor cells and macrophages, both of which were stained. Both of the stains, particularly NSE, detected more cells than lysozyme. With NSE, epithelia were often densely stained, and tumors with single cell infiltration were often impossible to assess for macrophage content. AP stained tumor and epithelial cells less strongly than NSE but often produced a fine granular positivity within them. (18 Refs)

121. STUDIES ON IN-VIVO PRIMING OF THE TRINITROPHENYL-REACTIVE CYTOTOXIC EFFECTOR-CELL SYSTEM. III. ARE HELPER T CELLS INVOLVED IN THE IN-VITRO GENERATION OF CROSS-REACTIVE AS WELL AS RESTRICTED CYTOTOXIC RESPONSES?

Fujiwara H, Levy RB, Shearer GM
Immunology Branch, NCI, NIH, Bethesda, MD, 20205
Immunobiology; 160(5):472-478 1982

The present study investigates the role of helper cells from trinitrophenyl(TNP)-primed mice in the generation of cytotoxic T lymphocytes (CTL) which lyse TNP-modified syngeneic (TNP-self) targets and cross-reactively lyse TNP-allogeneic target cells. Anti-TNP CTL activities generated from primed (either by intraperitoneal injection of TNP-syngeneic cells or by skin painting with trinitrochlorobenzene) and unprimed spleen cells were compared. When effector populations with comparable lytic activities on TNP-self targets were tested against allogeneic TNP-modified targets, only the in vivo primed effector cells displayed significant cytotoxicity. Since radioresistant helper cells have been found to enhance the anti-TNP-self CTL response, the question was raised whether this helper population could be shown to be involved in the enhanced TNP-allogeneic cross-reactive lysis. Normal spleen cells co-cultured with radioresistant helper cells failed to induce any detectable lysis on TNP-allogeneic targets under conditions for which these helper cells did enhance the lysis detected on TNP-self targets. These results suggest that triggering of such TNP-cross-reactive effector cells during the in vivo priming stage is responsible for the in vitro generation of cross-reactivity. (Author abstract) (17 Refs)

122. HUMAN COLONY-STIMULATING FACTOR PRODUCING CELL LINE.

Okabe T, Ohsawa N
Third Dept. Internal Medicine, Faculty Medicine, Univ. Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113, Japan
Cell Mol Biol; 27(6):579-587 1981

Colony-stimulating factor (CSF) is considered to be a physiological granulopoietin which controls differentiation of precursor cells into granulocytes or macrophages. The studies on human CSF have been hampered by the difficulty in obtaining the material in large quantities for purification. In 1974, a human CSF-producing tumor was successfully transplanted into athymic nude mice and maintained by serial passages. Human CSF-producing tumors maintained in nude mice served as a constant source for the purification of human CSF, but its usefulness was limited by the small size of the tumors obtained from the nude mice. From these tumors grown in nude mice, human CSF-producing cell lines have been established, and large-scale production of human CSF has become possible by the use of the cultured medium of the cells. The partially purified CSF in large quantities may serve as a standard human CSF, thus facilitating the further extensive studies on human CSF. It is our goal that the human CSF may serve as a therapeutic drug against neutropenia and other hematological disorders such as myelogenous leukemia. (Author abstract) (46 Refs)

123. A GROWTH FACTOR PRODUCED BY WEHI-3 CELLS FOR MURINE HIGH PROLIFERATIVE POTENTIAL GM-PROGENITOR COLONY FORMING CELLS.

McNiece IK, Bradley TR, Kriegler AB, Hodgson GS
Biological Res. Unit., Cancer Inst., 481 Little Lonsdale St., Melbourne, Victoria, Australia 3000
Cell Biol Int Rep; 6(3):243-251 1982

Preparation and properties of 'synergistic activity' (SA), a hemopoietic growth factor, from media conditioned by a myelomonocytic leukemic cell line (WEHI-3) are described. SA was prepared in high yield by conditioning serum-free medium with WEHI-3 cells that had been grown in vivo (BALB/c mice). SA was shown not to be stored in WEHI-3 cells. Storage at 4C and-20 C did not affect the activity. SA was stable between pH 2.0 and 10.6 and to heating for 1 hr at less than or equal to 50 C, but was unstable to storage at room temperature, trypsin digestion, 8 M urea with and without 4 milliM mercaptoethanol (ME) at pH 8.0, and to ME alone. Instability in the presence of ME indicated the presence of a disulfide bond, while inactivation by trypsin suggested that SA is a protein. The apparent mol wt was 9,000-25,000, and the isoelectric point was at pH 4.0-6.5. SA did not bind to concanavalin-A Sepharose. Morphologic studies showed that all colonies contained virtually pure populations of macrophages. (10 Refs)

124. NATURAL KILLER CELLS DO NOT BELONG TO THE RECIRCULATING LYMPHOCYTE POPULATION.

Zoller M, Bellgrau D, Axberg I, Wigzell H
Dept. Immunology, Biomedicum, Univ. Uppsala, Box 582, S-751 23 Uppsala, Sweden
Scand J Immunol; 15(2):159-167 1982

Natural killer (NK) cells constitute a cell type with an as yet undefined lineage, although certain similarities with T lymphocytes have been found in the mouse. Our present results show that NK cells have a significant difference compared with T and B cells in their capacity to traverse the blood-lymph barrier. Thoracic duct lymphocytes from mice or rats are thus devoid of NK activity, when at the same time potential, cytotoxic T lymphocyte (CTL) activity or antibody-dependent cellular cytotoxicity function can be demonstrated. Chronic thoracic duct drainage in the rat also leads to an increase in NK activity per unit cell number in the other lymphoid organs. Thoracic duct lymphocytes from mice and rats may thus serve as convenient sources of CTL and/or killer cells in situations in which it is important to minimize NK cell involvement. (Author abstract) (43 Refs)

CMI METHODOLOGY

125. METHOD DEVELOPED FOR RADIOSENSITIVITY EXAMINATION OF T-HELPER CELLS.

Temesi A, Pellet S

'Frederic Joliot-Curie' Natl. Res. Inst. Radiobiology and Radiohygiene, P. O. Box 101, H-1775 Budapest, Hungary

Stud Biophys; 86(1):79-80 1981

Deterioration of radiosensitivity of T-helper cells was studied in vivo in BD2F1 hybrid mice injected with thymus and sheep erythrocytes after 850 R Co-60 gamma-irradiation. Antibody forming ability of spleen cells was measured. Different subpopulations of T-cells manifested helper and suppressor function. Results showed that suppressor function of T-cells following 150-250 rad decreases to such an extent that function activity of T-helper cells is increased. Following 450 rad irradiation, injury of T-helper cells was observed. (3 Refs)

126. REGULATION OF THE COLONY-STIMULATING ACTIVITY PRODUCED BY A MURINE MARROW-DERIVED CELL LINE (H-1).

Garnett HM, Cronkite EP, Harigaya K

(c/o Cronkite) Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973

Proc Natl Acad Sci USA; 79(5):1545-1548 1982

The production of molecular species that stimulate growth of granulocyte or macrophage colonies (GM-CSF) by the fibroblastoid H-1 cell line is unaffected by either native or iron-saturated lactoferrin, although some inhibition is detected with 10 uM prostaglandin E1. The H-1 GM-CSF is able to support the formation of macrophage, neutrophil, and mixed colonies. Feeder layers of H-1 cells are also able to support the development of colony-forming units stimulated by GM-CSF (GM-CFUc) although the number of colonies produced when the optimal H-1 cell concentration is plated (2.5 x 10(3) cells) is only 30% of the number with conditioned medium alone. This inhibitory effect is observed irrespective of the presence of an additional agar layer between the feeder cells and plated bone marrow cells, implying that diffusable substances are involved. Addition of indomethacin (10 uM) to feeder layers derived from 2.5 x 10(3) H-1 cells increases the number of GM-CFUc detected to 50% of that seen with conditioned medium alone. This result suggests that released prostaglandin may be responsible for some, but not all, of the observed inhibition of colony formation. In the presence of the H-1 feeder layers, only macrophage colonies are detected and hence it appears that the H-1 cells produce, in addition to prostaglandin, a diffusible inhibitory substance that preferentially inhibits granulopoiesis. (Author abstract) (28 Refs)

127. SEROLOGIC IDENTIFICATION OF EARLY MEMBERS OF THE T CELL LINEAGE.

Berman JW, Basch RS

(c/o Basch) Dept. Pathology, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016

J Immunol; 128(4):1718-1722 1982

The SC-1 antigen, identified by thymus-absorbed rabbit anti-mouse brain antiserum, is present on multipotential stem cells. Its presence on cells of the T lineage has been examined by immunofluorescence, and we have demonstrated that it is also a marker for thymic development. Although it is present on the majority of fetal and neonatal thymocytes, its expression declines rapidly and, as early as 1 mo after birth, adult levels are reached. In normal animals, these do not change during adult life, even in mice destined to develop a T cell leukemia. SC-1 does reappear transiently on cells in the regenerating thymus of sublethally irradiated mice. Although the antigen is not associated with preleukemic changes in the thymus, it is expressed on some cells of all spontaneous T lymphomas, and it is uniformly present on tissue culture lines of cell lymphomas. (Author abstract) (11 Refs)

128. GROWTH OF HUMAN T LYMPHOCYTE COLONIES FROM WHOLE BLOOD: CULTURE REQUIREMENTS AND APPLICATIONS.

Knox SJ, Wilson FD, Greenberg BR, Shifrine M

Lab. Energy-Related Health Res., Univ. California, Davis, Davis, CA, 95616

J Cell Biochem; 18(1):15-24 1982

Colonies of T-lymphocytes were obtained from mitogen-stimulated whole blood (WB) cultures from 15 normal adults and 14 patients with hematologic diseases (4 Fanconi's anemia, 2 beta-thalassemia, 1 with active multiple myeloma (MM) and 1 with MM in remission, 3 acute myeloid leukemia, 1 chronic myeloid leukemia, 2 chronic lymphocytic leukemia). The conditions for optimal colony formation were stimulation with phytohemagglutinin (PHA) and/or concanavalin A (Con A); the use of WB rather than Ficoll-paque isolated lymphocytes, and plating at least 5,000 cells (50,000-100,000 cells for best results). This method was a more sensitive assay of responses to low doses of x-rays than 3H-thymidine uptake assays. The cloning efficiencies and radiation responses of PHA and/or Con A-stimulated T-cells from the patients with hematologic diseases often differed from patterns observed in the corresponding subpopulations of normal cells. WB cultures from larger groups of patients in each disease category are needed to evaluate these preliminary findings. It is concluded that the WB colony assay may have wide application to studies on cellular and clinical immunology. It may become useful as an additional diagnostic/prognostic indicator for certain diseases. (21 Refs)

SUPPRESSOR CELL ACTIVITY

129. A CLONED T-CELL LINE FROM A TOLERANT MOUSE REPRESENTS A NOVEL ANTIGEN-SPECIFIC SUPPRESSOR CELL TYPE.

Heuer J, Bruner K, Opalka B, Kolsch E
Dept. Immunology, Univ. Munster, Domagkstrasse 10, 4400 Munster, W. Germany
Nature; 296(5856):456-459 1982

Two major alternative models, clonal deletion and suppression, have been proposed as possible explanations for immunological tolerance. We have now isolated a functional T suppressor (Ts) cell clone to analyze the role of Ts cells in the induction and maintenance of tolerance. This cloned, long-term cultured Ts cell line (HF1) was derived from CBA/J mice (H-2k) in which low-zone tolerance (LZT)(3) had been induced by subimmunogenic doses of bovine serum albumin (BSA). HF1 cells show BSA-specific suppressor activity in two in vitro suppressor assays. HF1 Ts cells and a factor derived from them suppress unprimed, carrier-specific T helper (Th) cells in an assay measuring IgG antibody production against fluorescein-conjugated BSA (Flu-BSA). Furthermore, they block DNA synthesis in an antigen-specific in vitro T-cell proliferation assay. Their proliferation in the presence of antigen-presenting cells is antigen specific and shows restriction to the I-Ak region of the major histocompatibility complex (MHC). In addition, HF1 Ts cells have a characteristic cytotoxic activity. The data reported suggest that clonal deletion and suppression models are not necessarily mutually exclusive. Clonal deletion could manifest itself by the action of Ts cells. (Author abstract) (21 Refs)

130. AGE-DEPENDENT SEPARATION OF CLASS-SPECIFIC SUPPRESSOR CELLS IN THYMUS OF SJL/J MICE.

Clark DA, Cinader B, Koh SW
Dept. Medicine, McMaster Univ., Hamilton, Ontario L8N 3Z5, Canada
Immunol Lett; 3(4):189-194 1981

Thymocytes from young SJL/J mice (3-6 wk) contain suppressor cells that inhibit the antibody response of lymph node cells to sheep RBC. Effect of these suppressor cells disappears at age 24 wk or more. These aged animals acquire thymic suppressor cells which suppress the generation of cytotoxic T-cells, both in vivo and in vitro. While such suppressors are not present in the thymuses of young mice, suppression can be induced with estrogen and progesterone. The differentiation of functionally different suppressor cell populations in thymus may be affected by both age and hormonal status. (37 Refs)

131. CYCLOPHOSPHAMIDE-FACILITATED ADOPTIVE IMMUNOTHERAPY OF AN ESTABLISHED TUMOR DEPENDS ON ELIMINATION OF TUMOR-INDUCED SUPPRESSOR T CELLS.

North RJ
Trudeau Inst., Incorporated, Saranac Lake, NY, 12983
J Exp Med; 155(4):1063-1074 1982

An established methylcholanthrene-induced tumor, Meth A fibrosarcoma, was shown to completely and permanently regress in a syngeneic or semi-syngeneic host by combination therapy of iv injection on day 4 of tumor growth of 100 mg/kg of cyclophosphamide (CY) followed 1 hr later by iv infusion of splenic T cells from tumor immune donors. Infusion of immune cells alone had no effect on tumor growth and CY alone caused only a temporary halt in tumor progression. Most of the destruction of tumor caused by combination therapy was attributed to the antitumor action of passively transferred immune T cells. CY facilitates adoptive immunotherapy by elimination of a mechanism from the tumor-bearing host that normally prevents passively transferred tumor-immune T cells from expressing their antitumor function. The success of the combination therapy did not depend on the capacity of CY to reduce the tumor burden below a certain critical size. Failure of iv-infused, tumor-sensitized T cells to cause regression of the Meth A fibrosarcoma growing in syngeneic or semi-syngeneic hosts is caused by the presence of a tumor-induced population of CY-sensitive suppressor T cells. (13 Refs)

132. T LYMPHOCYTE-MEDIATED SUPPRESSION OF MYELOMA FUNCTION IN VITRO. IV. GENERATION OF EFFECTOR SUPPRESSOR CELLS SPECIFIC FOR MYELOMA IDIOTYPES.

Abbas AK, Takaoki M, Greene MI
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Exp Med; 155(4):1216-1221 1982

BALB/c mice were injected iv with viable syngeneic splenocytes to which affinity-purified M315 IgA was coupled developed suppressor T cells (Ts1) that inhibited IgA plaque-forming cells (PFC) after greater than 2 days in culture. On the other hand, T cells induced by soluble extracts of Ts1 cells (TsF1) and sc immunization suppressed greater than 50% of the PFC within 1 day and 80-90% by day 4. The cells mediating rapid suppression were operationally termed effector Ts. The specificity of the effector Ts was assessed by their ability to bind to different myeloma proteins. Suppressive activity was depleted by absorbing effector Ts on dishes coated with M315 IgA but not on dishes coated with MPC11 (IgG2b,k of unknown specificity) or M460 proteins. M315-specific effector Ts did not inhibit MPC 11 cells and caused greater than 70% selective suppression of IgA secretion by the MOPC 315-MPC11 somatic cell hybrid. Effector Ts were Thy-1.2+, Lyt-1-2+ cells, while Ts1 were either Lyt-1+2+ or T lymphocytes bearing both Lyt-1+ and Lyt-2+ markers were necessary for Ts1 to induce or mature into effector Ts in vitro. The ability to induce two cell types at different stages of a suppressor pathway, and to measure their effects on a monoclonal, autonomous target, should facilitate analysis of the differentiation and mechanisms of action of suppressor T lymphocytes. (11 Refs)

133. ENHANCED T CELL SUPPRESSION IS DIRECTED TOWARD SENSITIVE CIRCULATING B CELLS IN MULTIPLE MYELOMA.

Perri RT, Oken MM, Kay NE
Dept. Medicine, Hematology Section (111E), Veterans Admin. Medical Center, 54th St. and 48th Ave. South, Minneapolis, MN, 55417
J Lab Clin Med; 99(4):512-519 1982

Multiple myeloma, a disorder typically accompanied by monoclonal immunoglobulin excess and hypogammaglobulinemia was evaluated to delineate the status of T cell regulation on malignant B cell proliferation. Intact T cells and T cell subsets previously noted by us to be suppressor (Tgamma) and helper (T non-gamma) were isolated from 10 controls and 10 myeloma patients. Various concentrations of control and patient T cell subsets were mixed with control and patient B cells and stimulated with PWM. T cell effect on B cell proliferation as measured by [3H]thymidine incorporation was then determined. Myeloma Tgamma cells were more effective than control Tgamma cells in suppressing control or myeloma B cell [3H]thymidine incorporation. Interestingly, myeloma B cells, when added to myeloma Tgamma cells, were suppressed to a greater extent than were control B cells when mixed with a similar concentration of myeloma Tgamma cells. These in vitro studies suggest a complexity of B and T cell abnormalities in multiple myeloma; first, the myeloma B cells are extremely sensitive to Tgamma cell suppression, and second, myeloma Tgamma cells have excessive suppressor capacity. It is yet unclear whether these results are associated with an immunoregulatory response to this malignancy or represent part of the basic disease process. (Author abstract) (22 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abbas AK 132
Ablashi DV 16
Adams DO 105
Ades EW 65
Adler WH 53
Advani SH 109
Alonzo A 43
Anderson JR 7
Andersson TR 6
Andreeva NI 78
Angyal I 37
Appel SH 9
Arai H 77
Arima N 91
Armstrong GR 16
Arnaud P 65
Arvin A 39
Ashford NP 73
Askanas V 8
Astaldi G 31
Axberg I 124
Bakacs T 37
Balitskii KP 78
Baroni CD 27
Basch RS 127
Batsakis JG 113
Bellgrau D 124
Berman JW 127
Berney JJ 107
Bertram G 16
Bevan MJ 59
Bicker U 36
Binz H 47
Birshtein BK 92
Bjorkholm M 20
Blackman MA 82
Bloom BR 84
Blyth W 56
Bol SJ 107
Bom-Van Noorloo 4
Bonmassar E 55
Bonnard GD 86
Boorman GA 38
Bradley TR 123
Braun DP 29
Brostoff J 61
Broxmeyer HE 101
Brugiatelli M 31
Bruner K 129
Burakoff SJ 117
Burchardt K 2
Burk M 21
Bursuker I 96
Buzzi S 42
Caillol DH 66
Calder L 9
Campbell R 92
Capel PJ 116
Catovsky D 110
Centurioni R 1
Ceredig R 81
Chang KJ 41
Chapuis-Cellier 65
Cheever MA 62
Chevallier R 22
Cinader B 130
Clark DA 130
Cleton FJ 4
Cohen BB 90
Cohen M 99
Cohen MS 105
Cohen S 99
Coffier B 24
Colot M 18
Conkling PR 70
Conway TP 69
Costanza MC 102
Creegan WJ 15
Crichton D 90
Cronkite EP 126
D'Silva H 99
Dai Y 115
Dalakas MC 8
Dalal B 82
Daniel LW 60
Daniele RP 104
David CS 74
De Groot J 116
De Groot JW 108
De Heer E 108
De Jong WH 57
De Waal RM 116
DeBoer KP 29
Dean JH 38
Deane DI 90
Deeg HJ 45
Den Otter W 108
Diamond B 92
Donovan PA 98
Douglas KA 46
Dubreuil PC 66
Dullens HF 108
Dutton RW 89
Duval-Arnould B 15
Edwards A 26
Elgersma A 57
Engel WK 8
Engler H 71
Eremin O 7
Evans AE 12
Evans CH 54
Evans DL 60
Fache MP 51
Faggioni A 16
Fan DP 74
Fanciulli E 1
Favalli C 55
Fefer A 62
Fekete B 37
Festenstein H 43
Finkelstein MS 23
Fisher RI 3
Forman DS 15
Forrai I 37
Foster RS 102
Francis GE 107
Frendel E 51
Fujiwara H 121
Fujiwara K 52
Gamelli RI 102
Gangal SG 109
Garaci E 55
Garani T 33
Garnett HM 126
Gezzy CL 67
Gillis S 62
Gindhart TD 82
Giraudo Conesa 22
Goldman R 96
Goldstein AL 8
Golub SH 21
Goos M 14
Greaves MF 13
Greenberg BR 128
Greenberg PD 62
Greene MI 132
Gronberg A 83
Guastalla J 24
Guertin DP 74
Gustafson RO 30
Guy K 90
Hackman RC 45
Haines JW 93
Hale AH 60
Halliday WJ 48
Hardy JC 56
Harigaya K 126
Harris JE 29
Hart IR 98
Hecker E 100
Heise ER 33
Herr HW 5
Hersey P 26
Heuer J 129
Hewetson JF 16
Hilfiker ML 80
Hinson A 65
Hinuma Y 85
Hirano T 91
Hodgson GS 123
Holm G 20
Howard DR 113
Hsieh KH 41
Hu Y 115
Hudspith BN 61
Hui ZY 35
Hutchins D 90
Irons RD 49
Ishida T 52
Ishizaka T 84
Israel E 50
Ito M 77
Iwarson S 32
Jablonska S 34
Jezzi T 55
Johnson KJ 112
Kamaraju LS 16
Kaplan AM 97

Karre K 83
Kauffmann BM 46
Kay A 40
Kay NE 133
Keist R 100
Keller R 100
Kelly RB 9
Kemp A 26
Kibbelaar MD 116
Kiessling R 83
Kirchner H 71
Klassen DK 79
Klein A 17
Klein G 83
Klein GO 83
Klein JR 59
Kleinerman ES 25
Knox SJ 128
Koene RA 116
Koh SW 130
Kojima K 10
Kokoschka EM 18
Kolsch E 129
Konno K 77
Koppi TA 48
Koretzky GA 104
Koriyama K 9
Koshimura S 119
Kozak RW 19
Krensky AM 117
Kriegler AB 123
Krueger GR 16
Kruizinga W 57
Kumano N 77
Lane RD 97
Laufer TM 80
Leben L 43
Lemonnier FA 66
Leoni P 1
Lepault F 51
Levine PH 16
Levy RB 121
Lewis R 26
Li G 115
Liao Y 115
Lohmann-Matthes 94
Lozzio BB 44
Lozzio CB 44
Lum LG 11
Luster MI 38
Lydyard PM 61
Machado EA 44
Marcorelli E 27
Margolese RG 75
Mashkovskii MD 78
Mastro AM 106
McClure JE 8
McInnes J 26
McKimm-Breschki 58
McMurray DN 76
McNiece IK 123
Meier B 47
Meisterernst E 14
Melief CJ 4
Mellstedt H 20
Menezes J 16
Meuret G 111
Mickshe M 18
Mier JW 117
Migliorati G 55
Miller JF 58
Miskimen JA 74
Mitchell J 44
Miwa H 10
Mizel SB 64
Moghe MV 109
Montillo M 1
Montroni M 1
Moody CE 19
Moore M 88
Morgan EL 68
Moser K 18
Motomiya M 77
Mottram PL 58
Muchmore AV 25
Mugitani H 28
Munson AE 46
Murayama T 119
Nagai H 77
Naruki Y 28
Nash AA 73
Nash JR 120
Natsuume-Sakai 119
Neel HB 30
Neri A 31
Newsom-Davis J 9
North RJ 131
Nowell PC 104
O'Brien M 110
Ogenstad S 20
Ohsawa N 122
Ohtsuka S 28
Okabe T 122
Oken MM 133
Onoue K 91
Opalka B 129
Orita K 10
Ozger Topuz U 31
Paavonen T 114
Pal A 37
Palacios R 63
Palacios R 72
Parry H 61
Pasqualini RS 22
Pasternack MS 59
Pearson GR 16
Pearson GR 30
Pellet S 125
Pepin KG 106
Perri RT 133
Pfeifer RW 49
Phillips JP 7
Piacentini MJ 80
Plata F 118
Plowman PN 95
Polezhaeva AI 78
Poulik MD 69
Priest ND 93
Procopio A 27
Quan PC 84
Rainer H 18
Ransom JH 54
Rasmussen L 39
Raulet DH 59
Rebattu P 24
Reekers P 116
Reiss CS 117
Riabukhi VN 78
Rossi RB 55
Ruco LP 27
Ruitenberg EJ 57
Ryoyama K 119
Sagone AL 79
Sain LE 46
Sakaguchi A 52
Salvi A 1
Sanders VM 46
Sando JJ 80
Sato H 77
Satoh K 77
Saxena QB 53
Saxena RK 53
Scadding G 9
Schindler L 71
Schmidt W 43
Schneck J 92
Schumacher HR 15
Schwartz R 25
Seaman WE 82
Sesterhenn K 16
Shearer GM 121
Shifrine M 128
Shinbo T 28
Small M 87
Sondgrass MJ 97
Soubiran P 89
Staiano-Coico L 19
Steel CM 90
Steerenberg PA 57
Steigleder GK 14
Steinitz M 70
Sterry W 14
Storb R 11
Storb R 45
Strominger JL 117
Strong DM 15
Sugamura K 85
Sun G 115
Sundar SK 16
Suzuki M 28
Suzuki T 103
Svennevig JL 6
Swain SL 89
Szakal AK 97
Taffet SM 105
Takagi A 103
Takaoki M 132
Takayama H 103
Talal N 82
Talmadge JE 98
Tamir S 70
Tamura T 52
Tanaka Y 85
Tang SY 41
Tanigawa T 103
Tax WJ 116
Temesi A 125
Teranishi T 91
Thoman ML 68
Thomas ED 11
Thomas WJ 15
Thomas WR 58
Tindall RS 9

Tsurumi T 10
Tung TC 41
Ubels-Postma J 4
Uccini S 27
Van Beek AA 4
Van Heerde P 4
Van Heyningen V 90
Vanhaelen CP 3
Veksler IG 78
Viala JJ 24
Ville D 24
Vincent A 9
Von Dem Borne A 4
Vose BM 86
Vose BM 88
Wainberg MA 50
Wainberg MA 75
Walsh JD 67
Ward PA 112
Wedelin C 20
Weiden PL 45
Weigle WO 68
Weksler ME 19
Werb Z 82
Wetzel GD 89
White KL 46
Wigzell H 124
Wigzell H 47
Willcox N 9
Willems HW 116
Wilson FD 128
Witherspoon RP 11
Wust CJ 44
Xue Z 115
Yetley EA 76
Yoshida T 99
Yu M 50
Zeijlemaker WP 4
Zheng S 115
Zhou S 115
Zhu X 115
Zoller M 124
Zwelling LA 25

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CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
FRED RAPP Milton S. Hershey Medical Center	*The Interaction of Herpesviruses and Host Cells Leading to Latency or Transformation*	#VK05 52 min.
	Panel Discussion	#VK06 31 min.

MECHANISMS OF METASTASIS

ISAIAH FIDLER Frederick Cancer Research Center	*The Heterogeneous Nature of Cancer Metastasis and Implications for Therapy*	#VB01 47 min.
GEORGE POSTE Smith, Kline and French Laboratories	*Phenotypic Analysis of Metastatic Cell Populations*	#VB02 42 min.
LANCE LIOTTA National Cancer Institute	*Tumor Cell Invasion of Basement Membranes and Extracellular Matrices*	#VB03 33 min.
EVERETT SUGARBAKER Miami Cancer Institute	*Some Clinical Characteristics of Metastasis in Man*	#VB04 41 min.

AUTOMATED CYTOLOGY

Part One: Principles and Techniques	#VB05 56 min.
Part Two: Biological Applications	#VB06 52 min.

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Functional Aspects of Cellular Immunity

SERIES CB15 No. 82/09

SEPTEMBER, 1982

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In this issue:

- **EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS** **1-41**
- **EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS** **42-61**
- **EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION** **62-101**
- **THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE** **102-120**
- **ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY** **121**
- **RELATED BIOLOGY OF IMMUNE CELLS** **122-133**
- **CMI METHODOLOGY** **134-136**
- **SUPPRESSOR CELL ACTIVITY** **137-144**
- **OTHER RELATED STUDIES** **145-151**

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HE 20.3173/2:

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. CIRCULATING IMMUNE COMPLEXES IN MELANOMA PATIENTS TREATED WITH LEVAMISOLE FOLLOWING SURGERY.

Skeen MJ, Olkowski ZL
Lab. Tumor Biology and Clinical Immunology, Emory Univ. Sch. Medicine, Atlanta, GA
Rev Latinoam Oncol Clin; 13(5):5-15 1981

Circulatory immune complexes (CIC) were determined sequentially in 42 postsurgical melanoma patients to whom levamisole was administered as an adjunct immunotherapeutic agent. Immunocompetence parameters, including T lymphocyte quantitation, mitogenic stimulation, and lymphocyte antitumor cytotoxicity, were analyzed concurrently. The relationships of CIC to these parameters, to clinical status, and to immunotherapy were examined. Data indicated that elevated CIC may be found in a significant percentage of early stage melanoma patients. (36 Refs)

2. UNSPECIFIC IMMUNOLOGIC INVESTIGATION OF PATIENTS WITH MALIGNANT MELANOMA IN CLINICAL STAGES I OR II.

Knopf B, Watzig F
Hautklinik, Friedrich-Schiller-Universitat, Erfurter Strasse 35, DDR-6900 Jena, W. Germany
Dermatol Monatsschr; 168(1):24-33 1982

Immunological status was determined on 80 malignant melanoma (MN) patients after surgery. Fifty-seven of the patients (20 men, 37 women, 23-71 yr old) were in clinical Stage I, and 23 (8 men, 15 women; 32-70 yr old) were in clinical Stage II. Tests for immunological status consisted of counts of lymphocytes T and B; delayed hypersensitivity, using 2,4-dinitrobenzene (DNCB) and tuberculin (PPD); lymphocyte transformation by phytohemagglutinin (PHA), PPD, and DNCB; inhibition of leukocyte migration by PPD and DNCB; and measurements of serum IgA, IgG, IgM, and total complement. The tests were repeated 2-8 wk after surgery and every 3 mo for 2-4 yr. Results obtained with sera of the MM patients were similar to those of healthy controls (10 men, 20 women; 20-65 yr old). Neither prognosis nor relapse were indicated by the results of either the cellular or the humoral tests before clinical and/or radiographic symptoms appeared. The majority of the patients, who eventually had relapses, had from the start of the testing, negative results with the DNCB and PPD hypersensitivity tests and showed decreases in the stimulation of lymphocytes by PHA. MM patients without immunologic or histologic risk factors need not receive adjuvant therapy. (44 Refs) (In GER)

3. TREATMENT OF MALIGNANT GLIOMA WITH MUMPS VIRUS.

Yumitori K, Handa H, Yamashita J, Suda K, Otsuka S, Shimizu Y
Dept. Neurosurgery, Faculty Medicine, Univ. Kyoto, Kyoto, Japan
No Shinkei Geka; 10(2):143-147 1982

Six patients with malignant brain tumor were treated with mumps virus. Mumps virus was considered to be effective in three cases which were described in detail. First case: A 51-yr-old male with glioblastoma in the left thalamus was treated unsuccessfully with irradiation and chemotherapy after partial removal of the tumor. Mumps virus was administered, and 3 wk later showed 62% decrease of the tumor. Fifteen mo have passed since the treatment was started and the patient is still alive. Second case: A 46-yr-old male with a tumor in the corpus callosum was irradiated without operation. There was a 95% increase of the tumor. Mumps virus was administered, the tumor disappeared almost completely. The patient died 1 yr after the treatment was started, and death is ascribed to the metastatic lesion in the posterior fossa. Third case: An 18-yr-old female had a mass lesion in the left frontal lobe adjacent to the anterior horn of the lateral ventricle. Partial removal was performed and histological diagnosis was a mixed glioma consisting of ependymoma and oligodendroglioma. She was treated with mumps virus alone postoperatively. Follow-up CT scans showed an almost complete disappearance of the tumor. In the third case, administration of mumps virus alone induced an almost complete disappearance of the tumor on CT scans and improvement of clinical state. No effect of mumps virus was observed in other cases. The mechanism how mumps virus acts on tumor-bearing patients is not established but immunological effect appears to be most likely. Several immunological parameters such as NK cell, killer T-cell, suppressor T-cell function and specific reaction to TSA will be examined. (9 Refs) (In JPN)

4. IMMUNOLOGICAL PROFILE OF PATIENTS WITH TRANSITIONAL CELL CARCINOMA OF THE BLADDER.

Mukamel E, Shohat B, Servadio C
(c/o Servadio) Dept. Urology, Beilinson Medical Center, Petah Tiqva, Israel
Br J Urol; 54(1):11-15 1982

The immunological profile of 58 patients with various stages of transitional cell carcinoma of the bladder was determined by using the local xenogeneic graft versus host reaction (GVHR) test, by skin testing with 3 recall antigens (candida, trichophyton, streptokinase-streptodornase) and by quantification of T-lymphocytes. Thirty-two patients with low grade low stage tumors (Group A) showed only a slight impairment of the immunological profile with a slight decrease in T-lymphocytes, 4.4% negative GVHR tests and 31.2% negative skin tests. Ten patients with highly invasive inoperable tumors (Group B) showed a severe impairment of the immunological profile with a significant decrease in T-lymphocytes, 100% negative GVHR and 80% negative skin tests. A marked improvement in the immunological profile was noted while comparing nine patients who were examined within 6 mo after cystectomy (Group CI) (severe decrease in T-lymphocytes 44.4% negative GVHR tests and 66.6% negative skin tests) with seven patients who were examined 18 mo or more after operation (Group CII) (slight decrease in T-lymphocytes 0% negative GVHR and 42.8% negative skin tests). Incubation of T-lymphocytes with a thymic hormone (THF) caused an increase in the extent of the graft versus host reaction in 10 out of 14 patients with low grade low stage bladder tumors. This may represent an improvement in the functional activity of the T-lymphocytes with a possible therapeutic use in the future. (Author abstract) (22 Refs)

5. ROLE OF IMMUNOTHERAPY IN COMPLEX TREATMENT OF LUNG CANCER.

Trapeznikov NN, Gorodilova VV, Babakova SV, Kadagidze ZG, Trakhtenberg AKh, Mar'in ND, Drakina LV, Boguslavskii VM
No affiliation given
Vopr Onkol; 28(2):51-56 1982

The results of clinical trials of the efficacy of immunotherapy in lung cancer (LC) patients are reported. Evaluation of the immune status of 117 LC patients showed significant inhibition of the functional activity of immunocompetent cells. The degree of inhibition of cellular immunity was directly related to the Stage of LC. Efficacy of intrapleural administration of BCG vaccine was studied in 48 patients with Stage I-III LC. The patients were randomized into two groups. Group 1 (23) received preoperative immunotherapy with BCG vaccine and isoniazide (100 mg, tid, for 12 wk). Group 2 (25) underwent surgery alone (control). Side-effects of immunotherapy included transient fever, fatigue, and loss of appetite. The 2-yr survival rates after BCG immunotherapy were 100% for Stage I, 90.1% for Stage II, and 56.6% for Stage III, compared with 85.4%, 72.8%, and 40.1%, respectively, after surgery alone. (8 Refs) (In RUS)

6. IMMUNOREGULATORY CIRCUITS IN MYELOMA.

Ullrich S, Zolla-Pazner S
Dept. Pathology, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016
Clin Haematol; 11(1):87-111 1982

Studies on the mechanisms by which malignant plasma cells depress host immune response in myeloma are reviewed. Ig secreted by plasma cells feeds back via the immune network, causing expansion and suppression of clones of cells that regulate the humoral response. Other plasma cell secretions mediating the immune response include osteoclast activating factor, interferon, and PC-factor. Plasma cell Ig secretion can be altered by T cells specific for myeloma idiotype, for antigens, or for receptors. (88 Refs)

7. IN VIVO SENSITIZATION TO TUMOR-ASSOCIATED ANTIGENS IN PATIENTS WITH PROSTATIC CANCER (MEETING ABSTRACT)

Ablin RJ, Talluri K, Bhatti RA, Guinan PD, Banti G
Cook County Hospital, Chicago, IL, 60612
Proc Am Assoc Cancer Res; 23:983 1982

Initial studies have demonstrated the presence of cell-mediated immunity (CMI) to presumptively identified prostatic tumor-associated antigens in patients (pts) with prostatic cancer (PCa). Evaluated by tube leukocyte adherence inhibition this initial study of 53 PCa pts has been extended to 312 pts. Peripheral blood leukocytes (PBL) from PCa pts and 192 controls (including 91 pts with benign prostatic hypertrophy) were reacted with 3M KCl (NH(4))2SO4 extracts of allogeneic malignant prostate (specific extract). Pts and control PBL were also reacted (pending their availability) with extracts of normal and/or benign prostate as sources of non-specific extracts. Assessment of the immunoreactivity of PCa pts PBL was based on their percent of non-adherent cells obtained with each of the extracts as counted in quadruplicate, by the non-adherence index (NAI) and the significance (P) of the difference in the reactivities obtained between the extracts and pt and control PBL. The mean +/- SE per cent non-adherent cells obtained were 27.4+/-3.3 with malignant vs 10.3+/-0.9 normal (NAI 166, P less than 0.05) and 6.5+/-1.0 benign (NAI 322, P less than 0.05). The mean +/-SE percent non-adherent cells of 27.4+/-3.3 obtained between malignant prostate and PCa pts PBL differed significantly from that of 14.9+/-2.4 obtained for the reactivity of the control PBL. When evaluated according to their stage of malignancy, variable degrees of significant reactivity with malignant prostate were noted in each stage. A significant difference was noted between Stages A vs C, but not between the other stages. These results confirm and extend our initial observations of tumor-associated CMI in pts with PCa. (1 Ref)

8. PRIMARY PULMONARY HISTIOCYTOSIS X IN TWO PATIENTS WITH HODGKIN'S DISEASE.

Sajjad SM, Luna MA
Dept. Pathology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Thorax; 37(2):110-113 1982

The lungs may be involved in patients with histiocytosis X as part of the generalized disease, but histiocytosis X confined to the lung without extrapulmonary involvement is rare. This report describes two cases of primary pulmonary histiocytosis arising in patients with Hodgkin's disease. It is impossible to state with certainty whether the pulmonary histiocytosis arose as a response to the defect of cell-mediated immunity, or as a consequence of immunosuppression by radiation and chemotherapy. (Author abstract) (20 Refs)

9. NONSPECIFIC IMMUNE RESPONSE IN HODGKIN'S DISEASE.

Rytwinski K, Schneiberg K, Szelc S, Kolosza Z, Tabenska J
Oddzial w Gliwicach, Instytut Onkologii, ul Wybrzeze Armii Czerwonej 15, 44-101 Gliwice, Poland
Nowotwory; 31(3/4):181-190 1981

The nonspecific immunity was investigated in 58 patients (31 men and 27 women, 17-69 yr old) with Hodgkin's disease before treatment. Stage I according to the Ann Arbor Classification was established in 6 patients, II in 25, III in 18 and IV in 9. The histological classification revealed lymphocyte predominance in 7 patients, nodular sclerosis in 28, mixed cellularity in 18 and lymphocyte depletion in 5. The IgA, IgG and IgM levels were significantly increased and the percentage T cells was reduced in the entire group compared with 25 healthy controls. The absolute total lymphocyte count, lymphotoxin activity, phytohemagglutinin-induced blast transformation, and the percentage of positive dinitrochlorobenzene (DNCB) skin tests were reduced significantly. The decrease in the functional efficiency of the lymphocytes in the blast transformation tests, in the lymphotoxin activity, and the impairment of the response to DNCB were most pronounced in the patients in Stages III and IV, which suggests a positive correlation of these parameters with the clinical course of the disease. Positive correlation was found between the results of the DNCB skin test and blast transformation. A drastic decrease of both parameters was observed in the patients with lymphocyte predominance and the reduction of the T cell count was greatest in the patients with mixed cellular type. (30 Refs) (In POL)

10. DEFICIENT HELPER T CELL ACTIVITY IN NON-HODGKIN'S LYMPHOMAS (MEETING ABSTRACT)

Silver BA, Bostick-Bruton FW, Young RC, Fisher RI
Medicine Branch, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:991 1982

The observations that lymphomas are more common 1) after organ transplantation and immunosuppressive therapy, and 2) in certain autoimmune diseases suggest that altered immunoregulation may play a role in lymphoma pathogenesis. Thus, we investigated regulatory T cell function in the peripheral blood in 13 untreated adult non-Hodgkin's lymphoma patients and 13 age and sex matched controls. Six patients had nodular lymphomas, 7 diffuse. Nine had B cell tumors. No known T cell tumors were studied. Control mononuclear leukocytes (MNL) had greater proliferative responses to pokeweed mitogen (PWM) than patient MNL. MNL were separated into T and non-T fractions by two sequential neuraminidase-E-rosette sedimentations. Non-T cells were unresponsive to PWM. Responses of normal and patient T cells were similar. When normal non-T and autologous irradiated (3000R) T cells were cocultured, the response exceeded the response of patient non-T and autologous irradiated T cocultures. When normal non-T cells were cocultured with patient irradiated T cells, their response was diminished. Moreover, when patient non-T cells were cocultured with normal irradiated T cells, their response was enhanced. Normal non-T cell responses were the same regardless of whether autologous or normal allogeneic irradiated T cells were used as helpers. These results suggest that peripheral blood T cells from patients with non-Hodgkin's lymphoma are deficient in helper capacity for non-T cell blastogenic response to PWM and that patient non-T cells may have a normal proliferative response in the presence of normal allogeneic (helper) T cells. Abnormal immunoregulatory cell function may be important in the pathogenesis of the non-Hodgkin's lymphomas. (no Refs)

11. INTRAPERITONEAL IMMUNOTHERAPY OF HUMAN OVARIAN CARCINOMA WITH CORYNEBACTERIUM PARVUM (MEETING ABSTRACT)

Bast RC, Berek JS, Obrist R, Griffiths CT, Berkowitz R, Hacker NF, Parker L, LagasseLD, Knapp RC
Sidney Farber Cancer Institute, Boston, MA, 02115
Proc Am Soc Clin Oncol; 1:C-150 1982

Direct contact between immunostimulants and tumor cells has favored effective immunotherapy in animal models and clinical trials. In previous studies of a murine ovarian carcinoma, IP administration of C parvum inhibited IP tumor growth and augmented the activity of peritoneal cells for antibody dependent cell mediated cytotoxicity (ADCC). Doses and schedules of C parvum that augmented ADCC also potentiated serotherapy with specific rabbit heteroantiserum. C parvum (0.25-4.0 mg/m(2)) has been administered IP on 1-8 occasions to 11 patients with peritoneal implants of ovarian carcinoma that had failed to respond completely to cytoreductive surgery and combination chemotherapy. An additional 2 patients have been treated in an adjuvant setting following a complete response to chemotherapy. Fifty-one courses of IP immunotherapy have been assocated with fever greater than 101 F (25%), abdominal pain (88%), nausea (57%), vomiting (29%) and hypotension (6%). Of 11 patients with residual disease, 8 have been treated for a sufficient period to evaluate response. Among these 8 patients, 2 have had complete responses (5 and 12 mo), 1 a partial response, 2 stabilizaiton of disease and 3 disease progression. Administration of C parvum IP has augmented the ability of human peritoneal cells to lyse human ovarian carcinoma cell lines in the presence of specific rabbit heteroantiserum. C parvum administered IP appears to inhibit the growth of human ovarian carcinoma and may prove useful for modulating the activity of human effectors of ADCC. (no Refs)

12. NATURAL KILLING (NK) OF K56 ERYTHROLEUKEMIA CELLS IN HODGKIN'S DISEASE PATIENTS (MEETING ABSTRACT)

Kamiya H, Lange B, Starr S
Department of Pediatrics, Mei University School of Medicine, Mei, Japan
Proc Am Soc Clin Oncol; 1:C-614 1982

Peripheral blood mononuclear cells from 25 children and adolescents with Hodgkin's disease (median age, 14 years) were tested for their spontaneous ability to kill (NK) erythroleukemia target cells of the K562 line. NK activity was measured by release of Cr51 after 3 hr in culture at an effector to target ratio of 25:1. NK activity of 6 of 9 patients receiving chemotherapy or irradiation within the previous 2 months was lower than that of 42 healthy age-matched controls. Three patients receiving therapy and 8 who had discontinued therapy showed normal NK activity. NK activity of 5 patients who had discontinued therapy was higher than normal. These preliminary results suggest that cytotoxic therapy inhibits NK activity, and cessation of therapy is associated with a rebound to normal or supranormal levels of NK in Hodgkin's disease patients. (no Refs)

13. HELPER T-CELL FACTOR IN SERUM FROM PATIENTS WITH NON-HODGKIN'S MALIGNANT LYMPHOMAS (MEETING ABSTRACT)

Chartrand SL, Gajl-Peczalska KJ
University of Minnesota, Minneapolis, MN, 55455
Fed Proc; 41(3):335 1982

T cell fraction (mean 97% E-rosette forming cells) was obtained from peripheral blood of healthy volunteers. T cells were cultured separately for 5 days with 50% serum from 13 newly diagnosed patients with non-Hodgkin's malignant lymphomas, 50% serum from allogeneic normal control donors and 50% fetal calf serum (FCS). T cells were then mixed with allogeneic tonsillar B lymphocytes, stimulated with pokeweed mitogen, and after 12 day cultures the IgA, IgG and IgM secretion was measured by double-antibody radioimmunoassay. It was found that the serum from approximately 70% patients with B cell lymphomas enhanced helper T cell function when compared to serum from normal individuals. The highest enhancing effect, expressed as a n-fold increase of Ig secretion with T cells precultured in patient versus control serum, was found in IgG production; it was somewhat lower for IgA, and the lowest for IgM. Ig secretion with T cells precultured with FCS was generally lower than with control human serum. Therefore the values calculated against T lymphocytes precultured in FCS were slightly higher, the mean for IgG being 9.8, for IgA 6.6 and for IgM 5.3. The attempts to characterize the enhancing factor present in the serum of lymphoma patients will be presented. (no Refs)

14. REDUCED NATURAL KILLER CELL ACTIVITY OF LYMPHOCYTES FROM PATIENTS WITH WERNER'S SYNDROME AND RECOVERY OF ITS ACTIVITY BY PURIFIED HUMAN LEUCOCYTE INTERFERON.

Goto M, Tanimoto K, Horiuchi Y, Kuwata T
Dept. Internal Medicine and Physical Therapy, Univ. Tokyo, Tokyo, Japan
Scand J Immunol; 15(4):389-397 1982

Natural killing (NK) activities were measured in peripheral blood lymphocytes (PBL) from 14 patients with Werner's syndrome (WS), and the results were compared with those of 187 normal individuals at different ages. The NK activities of healthy donors were demonstrated in a characteristic and invariable manner in accordance with the age and the sex, whereas the activities of WS patients were considerably reduced irrespective of the age and the sex. When normal PBL were preincubated with WS sera containing anti-lymphocyte antibodies (ALA) plus rabbit complement, the NK activities of the surviving PBL were markedly reduced when compared with those of PBL treated with other heterologous ALA of rabbit origin in the same manner. PBL from WS patients treated with purified human leukocyte interferon augmented the NK activity even beyond the range of controls. These results suggested that NK activities in WS patients were reduced in a manner similar to that in normal old individuals. The ALA reactive to NK cells in WS patients may participate in the reduction of NK activities. The augmentative effect of interferon on NK activities in WS patients may also suggest the possible blocking of potent NK activities by an unknown mechanism rather than an intrinsic defect of their NK cells. (Author abstract) (39 Refs)

15. STUDIES OF HUMAN NATURAL KILLER CELLS. I. IN VIVO PARAMETERS AFFECTING NORMAL CYTOTOXIC FUNCTION.

Pross HF, Baines MG

Dept. Radiation Oncology, Queen's Univ., Kingston, Ontario K7L 2V7, Canada

Int J Cancer; 29(4):383-390 1982

The results of natural killer cell (NK) studies on 539 normal healthy donors tested from once to 213 times over a 7-yr time span have been presented. NK activity did not vary with donor blood group, Rh type or (in a small sample) HLA type. There was a slight but significant increase in NK activity from birth to adulthood, and between males and females. The male/female difference was present at birth and persisted through adulthood. The relative NK activity of individual donors tested repeatedly over many yr was remarkably consistent in spite of variability in the absolute cytotoxicity observed. The expression of NK data in terms of relative NK was found to be superior to other methods, and the values obtained were found to be independent of the NK-sensitive target cell used. Although age and sex differences in NK activity are slight, their existence should be considered when studies of NK activity in patients are analyzed. (Author abstract) (20 Refs)

16. DEFECTIVE NK ACTIVITY OF HUMAN OVARIAN TUMOR-ASSOCIATED LYMPHOID CELLS: LOW NUMBERS OF EFFECTORS ARE PRESENT IN SITU (MEETING ABSTRACT)

Allavena P, Introna M, Colombo N, Mantovani A

Istituto di Ricerche Farmacologiche, Mario Negri, Milano, Italy

Fed Proc; 41(3):599 1982

This study was designed to elucidate the mechanisms involved in the defective NK (natural killer) activity of tumor-associated lymphocytes (TAL) in human ovarian carcinoma. Lymphoid cells were separated from 15 ascitic and 2 solid tumors on discontinuous Ficoll-Hypaque. NK activity was measured against K562 target cells in a 4 or 20 hr 51Cr release assay. Purified preparations of TAL usually had low levels of NK activity compared to autologous peripheral blood lymphocytes (PBL). NK effector cells in the blood have been morphologically identified as large granular lymphocytes (LGL). It was, therefore, of interest to evaluate the % LGL in the TAL and PBL of these patients. Purified TAL had a very low number of cells with LGL morphology (median 2%, range 0.1-10) while PBL had 10% median LGL (range 5-20). Percoll fractionated TAL and PBL gradients resulted in an enrichment of LGL in the lower density bands up to 40% in the TAL population, and 70-80% in the PBL. NK activity from PBL and TAL was also recovered in the low density cells and was 2-4 fold increased compared to the input populations. These data indicate 1) a positive correlation between LGL and NK activity also at the tumor site; 2) a low frequency of the relevant effector cells (LGL) is one of the major factors involved in the defective NK activity within human ovarian carcinoma. (no Refs)

17. NATURAL KILLER (NK) ACTIVITY AGAINST HUMAN PRIMARY SOLID TUMORS (PT) (MEETING ABSTRACT)

Serrate SA, Vose BM, Timonen TT, Ortaldo JR, Herberman RB

National Cancer Institute, National Institutes of Health, Bethesda, MD, 20205

Fed Proc; 41(3):601 1982

Human peripheral blood NK activity using adherent and non-adherent cell lines is mediated by a morphologically defined subpopulation, termed large granular lymphocytes (LGL). The present study examines the effector cells causing in vitro lysis of primary human tumor cells. Carcinomas of the lung, colon, breast, or neck; and melanoma were dispersed in collagenase, separated in discontinuous Ficoll gradients, and used as 51Cr-labeled targets. Adherent cells (AC), LGL and T cells (isolated from low and high density fractions of a discontinuous Percoll gradient) were isolated from PBL (peripheral blood lymphocytes), and tested in an 18 hr release assay. Using PBL, significant cytotoxicity was seen in 5/19 tests against PT, whereas LGL from the same donors had significant reactivity in 13/19 tests against PT. In contrast, no cytotoxicity was mediated by T cell or AC fractions against either PT or K562. Furthermore, the addition of T cells (50%) or AC (10%) to LGL-containing (greater than 60%) effector cells, did not cause a significant decrease in the reactivity in 3 donors when tested against 4 PT. These results indicate that the lysis of primary tumor by normal PBL is strongly associated with LGL. Thus, LGL may be involved in natural resistance against primary human tumors as well as tumor cell lines. (no Refs)

18. ROLE OF MONOMERIC IGG IN HUMAN GRANULOCYTE - MEDIATED CYTOTOXICITY OF TUMOR CELLS (MEETING ABSTRACT)

Korec S, Sulica A, Cannon GB, Herberman RB

Division of Medical Oncology, Vincent T Lombardi Cancer Research Center, Washington, DC

Proc Am Assoc Cancer Res; 23:1047 1982

Plasmagel (Pg) - separated granulocytes display a high degree of in vitro antitumor activity, as measured by a growth inhibition assay (GIA). More than 90% decrease in 3H-thymidine uptake by variety of human tumor (breast, lung myeloid leukemia) derived cell lines is reproducibly seen. This activity is almost completely abolished when granulocytes are separated by one-step, double gradient Ficoll-Percoll (FP) method. The finding that this defect can be corrected by addition of serum to the assay suggests the role of a serum-derived surface bound factor that may be lost during the FP separation procedure. Granulocytes have been previously shown to contain surface bound IgG, as measured by rosetting with Staphylococcal Protein A (SPA)-coated ox erythrocytes. While Pg granulocytes formed up to 10% such rosettes, almost none were found with FP-cells. To determine the role of surface-bound IgG in cytotoxicity, we tested monomeric IgG prepared by repeated G-200 fractionation. This fraction completely restored the FP granulocyte cytotoxicity. Perfusion over a column containing Sepharose-bound SPA did not influence the restorative potential, suggesting a major role of IgG-3. These data indicate that granulocyte mediated cytotoxicity of tumor cells is dependent on monomeric IgG most probably of the IgG-3 subclass. (no Refs)

19. AN IMMUNOREGULATORY MECHANISM IMPLICATED BY THE BLOCKING FACTORS IN SERUM FROM PREGNANCY.

Takeuchi S, Chang KS, Urushizaki I, Hosokawa M, Herberman RB, Aoki T
Dept. Obstetrics and Gynecology, Niigata Univ. Sch. Medicine, Asahimachi-Dori, Niigata, Japan
Excerpta Med Int Congr Ser; 576:147-165 1981

Pregnancy appears to result in induction of blocking antibodies (BA), which prevent immunological rejection of the fetus. Induction of BA seems to be linked to HLA-D determinants of the conceptus (embryo-trophoblast unit), with more BA produced with greater antigenic disparity. In aborters, habitual and one-time, a lack of BA has been implicated. In habitual aborters, one-way mixed lymphocyte culture was significantly depressed, but this was not true in one-time cases. In hydatidiform mole, continued production of BA after death of the fetus appears to allow development. The normal sequence of events would be a gradual decrease in BA, culminating in spontaneous abortion. These findings are related to Voisin's hypothesis on immunoregulation. Any cancer immunotherapy which induces BA might be detrimental and allow the cancer cells to escape immune detection and destruction. (41 Refs)

20. IMMUNOPOTENTIATING ACTIVITY OF LENTINAN.

Miyakoshi H, Aoki T, Usuda Y, Izumi T, Herberman RB, Chang KS, Sendo F
Res. Div., Shinrakuen Hosp., Niigatashi, Japan
Excerpta Med Int Congr Ser; 576:118-126 1981

The immunopotentiating activity of Lentinan was tested in was tested on human peripheral WBC both in vitro and in vivo by means of three in vitro assay systems. Lentinan weakly increased spontaneous 3H-thymidine (TdR) incorporation by peripheral blood lymphocytes (PBL), but only when T cells, B cells, and adherent cells were present. Lentinan increased 3H-TdR incorporation by suboptimal doses of the mitogens staphage lysate and concanavalin A (Con A), with very little effect with phytohemagglutinin. This mitogen-enhancing effect was also seen in cancer patients, who had reduced reactivity. Lentinan augmented pokeweed mitogen (PWM)-stimulated production of IgG and IgM, but at concentrations higher (1-100 ug/ml) than required for 3H-TdR incorporation stimulation. Lentinan abrogated the suppressive effect of Con A on PWM-stimulated IgG production by PBL. Lentinan had variable effects on cytotoxic activity of natural killer (NK) cells from healthy persons in vitro. In vivo it enhanced NK cell cytotoxic activity of a patient with lung cancer. This NK activity was higher in the presence of normal serum. These results are contrasted with previous work on Lentinan. (21 Refs)

21. LYMPHOMA IN CARDIAC ALLOTRANSPLANT RECIPIENTS. CLINICAL AND HISTOLOGICAL FEATURES AND IMMUNOLOGICAL PHENOTYPE.

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Transplantation; 33(4):347-351 1982

To characterize further lymphomas which arise in chronically immunosuppressed allotransplant patients, we studied the clinical and histological features of seven cases of nonHodgkin's lymphoma and determined the immunological phenotype in four cases, which developed in a series of 182 patients who underwent cardiac transplantation at Stanford University Hospital. Clinical features which were correlated with the development of lymphoma included patient age, pretransplant diagnosis, and the number of transplants. All cases of non-Hodgkin's lymphoma presented as solitary or multiple localized extranodal lesions while none presented in lymph nodes. Extranodal sites of involvement included brain, lung, and soft tissues of the thigh at the site of antilymphocyte serum injections. Histologically, five of seven lymphomas were classified as high grade, large cell, immunoblastic and two of seven as intermediate grade, large noncleaved cell. The immunological phenotype of the neoplasm from four patients was determined by reaction with immunoglobulin light and heavy chain reagents and monoclonal antibodies to T cell and B cell antigens. All lymphomas from four patients which were tested stained for Ia antigen (HLA-DR) but did not stain for immunoglobulin or the T cell antigens detected in this study. (Author abstract) (33 Refs)

22. LYMPHOMATOID GRANULOMATOSIS. AN ANALYSIS OF CLINICAL AND IMMUNOLOGIC CHARACTERISTICS.

Sordillo PP, Epremian B, Koziner B, Lacher M, Lieberman P
1275 York Ave., New York, NY, 10021
Cancer; 49(10):2070-2076 1982

Six patients with lymphomatoid granulomatosis were studied. Two patients had eye involvement, a rare manifestation of this disease. Both had complete disappearance of disease in this area after radiation therapy. One patient presented with an autoimmune hemolytic anemia, which remitted completely with chemotherapy. The use of corticosteroids or chemotherapy was effective in bringing about a decrease in pulmonary infiltrates in all six patients, although the duration of response was limited. One patient did have a prolonged period of clinical remission, and died of an unrelated cause. Evidence of profound immunologic abnormalities was found in these patients by a variety of tests. The extensive immunologic dysfunction present in patients with lymphomatoid granulomatosis has not previously been described. Most strikingly, patients with lymphomatoid granulomatosis have a severe impairment in T-lymphocyte function, confirmed by their inability to react to common skin test antigens or dinitrochlorobenzene, decreased in vitro lymphocyte responsiveness to mitogens and antigens and changes in T-cell subset populations. This may account for the frequent development of malignant lymphomas in patients with this condition. (Author abstract) (24 Refs)

23. ON THE RELATIONSHIP OF CELLULAR AND HUMORAL FACTORS OF IMMUNITY IN ACUTE LEUKEMIA.

Akimova GV, Osipov SG, Eremeev VS, Rumiantsev AG, Bergol'ts VM
P. A. Herzen Res. Inst. Oncology, RSFSR Ministry Health, Moscow, USSR
Vopr Onkol; 28(2):84-88 1982

The influence of autologous serum on cell reactions resulting in both blocking and potentiation was established in the study of serum factor effects on cell-mediated reactions in acute lymphoblastic leukemia. Statistically significant differences in both potentiating and blocking effects of autologous serum depending on therapeutic procedure were shown. (Author abstract) (12 Refs) (In RUS)

24. IMMUNOTHERAPY OF ACUTE MYELOCYTIC LEUKEMIA WITH NEURAMINIDASE MODIFIED MYELOBLASTS AS IMMUNOGEN (MEETING ABSTRACT)

Bekesi JG, Cuttner J, Holland JF, Silver R, Colman M
The Mount Sinai School of Medicine, New York, NY, 10029
Proc Am Soc Clin Oncol; 1:C-142 1982

We have previously demonstrated the therapeutic effectiveness of neuraminidase modified syngeneic and allogeneic leukemic cells as immunogen in the treatment of transplantable and spontaneous leukemia in mice. Based on these experimental observations, a successful chemoimmunotherapy trial was conducted in patients with AML (acute myelocytic leukemia). One hundred sixty-three previously untreated patients with AML were randomized in the chemoimmunotherapy study folowing successful remission induction using cytosine arabinoside and daunorubicin. In the group randomized to receive neuraminidase treated allogeneic myeloblasts or neuraminidase treated myeloblasts plus methanol extraction residue (MER), immunization was accomplished (id) every 28 days midway between the maintenance cycles of chemotherapy. Chemotherapy was terminated at 4 years and immunotherapy at 5 years of complete remission. The difference in remission and survival times between the treatment groups is highly significant: p less than .001, with a plateau which stretches 3 to 8.5 years. The addition of MER to the protocol eliminated the plateau phase of continuing remission duration observed in patients who received N'ase treated myeloblasts alone partially attributable to the associated appearance of suppressor monocytes. In vivo and in vitro immunodiagnostic tests indicate the restoration of normal immunocompetence in patients receiving neuraminidase modified allogeneic myeloblasts as immunogen and strongly suggest that patients with AML have an improved cell-mediated immune reaction to leukemia antigen. (no Refs)

25. EFFECT OF OPERATION ON PERIPHERAL LYMPHOCYTE COUNTS AND PRODUCTION OF ADENOSINE TRIPHOSPHATE (ATP) IN CANCER PATIENTS.

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J Surg Oncol; 20(1):1-8 1982

Lymphocyte bioenergetics in cancer patients undergoing surgery is largely unexplored. The effect of surgery on total lymphocyte counts and adenosine triphosphate (ATP) production is reported. Lymphocyte ATP was assayed by the coupled enzymatic method using hexokinase and glucose 6-phosphate dehydrogenase and lymphocyte counts were calculated from total leukocyte counts and differential counts. Lymphocyte ATP assay and counts were carried out in 13 patients pre- and postoperatively, and lymphocyte counts were scored in six more patients similarly. In 69% of the patients lymphocyte ATP production was depressed postoperatively, and this condition appeared to be associated with cancer spread and immunosuppressive tumors. Postoperative increase in lymphocyte ATP was observed following hysterectomy, colostomy, and also after blood transfusion. The significance of the findings are discussed. Changes in postoperative lymphocyte counts correlated with lymphocyte ATP in 62% of the cases. (Author abstract) (54 Refs)

26. SPECIFICITY OF AUTO-TUMOR CYTOTOXICITY EXERTED BY FRESH, ACTIVATED AND PROPAGATED HUMAN T LYMPHOCYTES.

Vanky F, Klein E
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Int J Cancer; 29(5):547-553 1982

The specificity of auto-tumor cytotoxicity exerted by patients T lymphocytes was investigated. Lymphocytes were used as effectors against freshly separated tumor cells. Activation was achieved by treatment with interferon (Hu-IFN-alpha), stimulation with PHA, co-cultivation with autologous tumor biopsy cells (ATS) and allogeneic lymphocytes (MLC). ATS was the most efficient in generating auto-tumor cytoxicity. In some cases the lymphocytes also damaged autologous tumor cells, but IFN-pretreatment of the lymphocytes had no such effect. When the ATS- or MLC-activated lymphocytes were propagated with conditioned medium known to contain Interleukin-2, their lytic potential against autologous tumors was maintained. On the population level, the ATS was specific for the autologous tumor cells. Cold target competition tests suggested that in the MLC-s the autologous tumor cells were killed by a distinct set of lymphocytes because allogenic cells did not compete. Thus, in these cultures the auto-tumor specificity of the lysis was on the level of the effector subset. Therefore, it is likely that, independently of the mode of activation, the auto-tumor lysis is the function of lymphocytes which recognize tumor- or organ-specific antigens on the target cells. (30 Refs)

27. IMMUNE MODIFYING EFFECTS OF CIMETIDINE ON LYMPHOCYTE FUNCTION IN CANCER PATIENTS AND CONTROLS (MEETING ABSTRACT)

Wanebo HJ, Pace R
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Proc Am Soc Clin Oncol; 1:C-172 1982

Cimetidine, an H2 antagonist is thought to have immunodulating effects on lymphocyte function in vitro and in animal tumor systems in vivo. An analysis of in vitro effects on mitogen and antigen induced lymphocyte blastogenesis was carried out in 20 control and 19 cancer patients who had depressed lymphocyte function. Cimetidine was incubated in concentrations in 10-3M to 10-8M. Lymphocyte blastogenesis curves were generated using multiple concentrations of phytohemagglutinin (PHA) or Staph Phage Lysate (SPL). Cimetidine was either co-incubated with the lymphocyte stimulant or was preincubated 48-72 hrs. Cimetidine produced significant increases of PHA response in (8/20) 40% and of antigen response in 13 of 16 (81%) normal controls. The response increases ranged from 15-161%. Patients with various cancers (colon, breast, head and neck), who generally had depressed responses, showed varying effects. PHA responses were depressed in 14 of 19 patients and increased in 2. Responses to SPL were increased in 9 of 10 patients tested (increase 12-65%). Cimetidine appears to have immune modifying capabilities in controls and in depressed patients with cancer, and is able to augment selected lymphocyte function tests in both groups. The effects are modest and highly dependent on concentration and type of stimulant. (no Refs)

28. PHASE I CLINICAL TRIAL OF INFUSION INTO CANCER PATIENTS OF AUTOLOGOUS LYMPHOCYTES ACTIVATED IN VITRO WITH LECTINS (MEETING ABSTRACT)

Mazumder A, Grimm EA, Eberlein T, Rosenberg SA
Surgery Branch, National Cancer Institute, Bethesda, MD, 20205
Proc Am Soc Clin Oncol; 1:C-158 1982

We have previously demonstrated that peripheral blood lymphocytes (PBL) of cancer patients can be activated by lectins to lyse fresh autologous tumor cells (FATC) but not normal cells in vitro. A clinical protocol has been instituted in cancer patients who had failed all other therapies to determine the toxicity and effects in vivo of the infusion of large numbers of autologous activated PBL. Eight patients have thus far been entered into the protocol, 5 sarcomas, 1 melanoma, 2 colorectal cancer. Up to 1.7x10(11) PBL were obtained from 9 to 14 successive leukaphereses and incubated in vitro in medium containing phytohemagglutinin (PHA) and human AB serum for 2 days and then reinfused following the next leukapheresis. Toxicity included fever and chills in 8/8 patients, headaches in 5/8, transient nausea and vomiting in 3/8 and a mean decrease of 30% in pulmonary diffusion capacity that reversed within 24 hours in 6/6 patients tested. Six of eight patients required 1 unit of RBC tranfusion. In 6/6 patients, highly activated PBL were found in the circulation by the sixth leukapheresis. The background incorporation of 3H-Tdr (thymidine) into PBL increased from 3 to 7 fold with successive leukaphereses and could be enhanced in vitro by the addition of lectin free T cell growth factor. PBL lytic for FATC also increased from 2% initially to 27% on successive fresh PBL collections in 6/6 tested. Thus far no significant clinical effects have been seen. Thus, it appears that large numbers of autologous PHA activated PBL can be safely obtained and infused into humans, achieving an increase in the number of circulating activated cells. (no Refs)

29. THYMOCYTOTOXIC ANTIBODIES IN PATIENTS WITH AUTOIMMUNE HEMOLYTIC ANEMIA, SYSTEMIC LUPUS ERYTHEMATOSUS AND LYMPHOPROLIFERATIVE DISEASES.

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Blut; 44(4):225-230 1982

Cytotoxic antibodies against thymocytes and peripheral blood lymphocytes were studied in patients with autoimmune hemolytic anemia (AIHA), active systemic lupus erythematosus (SLE), and lymphoproliferative diseases (LD). Sera of 66 patients were investigated: 25 with idiopathic and 8 with LD-associated AIHA, 23 with LD, and 10 with active SLE. The results of the cytotoxicity tests against thymocytes and T lymphocytes are summarized. The incidence of thymocyte antibodies (TA) was almost twice that of lymphocyte antibodies. No significant difference in the frequency of TA and T lymphocyte antibodies was observed in the single types of LD or between the patients with 'warm' or 'cold' AIHA. Only 42% of the sera containing TA were also reactive against T lymphocytes, whereas 70% of the sera cytotoxic for T lymphocytes were also thymotoxic. Thirty-six percent of sera were reactive against both thymocytes and T lymphocytes. Each serum contained antibodies directed against a different number of T lymphocyte samples without it being possible to statistically show specificities with particular HLA-A or B antigens. The percentage of cytotoxicity varied among the sera from patients with the same disease. The extent of thymocytotoxicity was always different from that of T lymphocytotoxicity for sera showing both reactivities. In both cytotoxicity tests for T lymphocytes and thymocytes, the percentage of variation of dead cell counts between duplicate assays was 5% or less. The distribution of dead cells in the thymocytotoxicity test in different diseases is presented. (25 Refs)

30. SEPARATION OF AN IMMUNOSUPPRESSIVE FACTOR FROM PLEURAL FLUID OF PATIENTS WITH LUNG CANCER (MEETING ABSTRACT)

Chang-Xue Z
Harvard Medical School, Boston, MA, 02115
Fed Proc; 41(3):417 1982

Impaired immunoresponsiveness is often seen in patients with advanced cancer. In this study, we observed that macrophages from patients with lung cancer showed a significantly lessened capacity to phagocytize erythrocytes as compared to that of macrophages from normal volunteers. However, one month after the removal of these tumors, the phagocytic activity of patients' macrophages was fully restored. Furthermore, pleural fluid was obtained from these patients before surgery and found to be able to inhibit the capacity of normal human macrophages to phagocytize erythrocytes, suggesting the presence of a suppressive factor(s) in the fluid. We subsequently purified the suppressive factor(s) from these fluids with gel electrophoresis. The suppressive effect was found in fractions of F4 and F5, corresponding to the molecular size of alpha-globulin and albumin, respectively. Therefore, the present findings suggest that a factor(s) active in inhibiting macrophage function was isolated from the pleural fluid of patients with lung cancer and that this factor might be similar to immunoregulatory alpha-globulin previously described. (no Refs)

31. NATURAL ATTACHMENT AND KILLING OF MALIGNANT TARGETS BY FRACTIONATED BLOOD LEUKOCYTES (MEETING ABSTRACT)

Brahmi Z, Lazarus K, Hubbard A, Bray R, Butterick C, Baehner R
Indiana University School of Medicine, Indianapolis, IN, 46223
Fed Proc; 41(3):601 1982

We devised a simple reproducible assay to quantitate the binding efficiency of unfractionated human mononuclear cells (MC). MC were separated into 5 fractions: Ficoll-Hypaque (uni), plastic adherence (macs) and 3 percoll density gradients (PI, PII, PIII). All the fractions were able to bind to the two target cells (TC) used with percentages averaging: uni 21, macs 23, PI 14, PII 11 and PIII 8. EM (electron microscopy) examination of various MT-TC aggregates including the NK enriched fraction revealed interdigitations in the areas of cell contact but no membrane fusion. When MC from two unrelated Chediak-Higashi patients were examined, binding was unimpaired although the NK mediated lysis was depressed. Treatment of NK cells with phorbol myristate acetate (PMA) inhibited completely NK lysis without impairing the binding or cell viability; following overnight incubation in the absence of PMA the cells did not regain their lytic activity. PMA treated TC lead to increased cytotoxicity. Finally, treatment of MC with PMA (150ng/ml, 5 min) generated only 5.65 nmoles/10(7) cells of O2, 40 times less than the PMN. Our results indicate that: (1) increasing percent of binding between NK enriched fractions and TC does not lead to increased lysis, (2) cytotoxicity mediated by NK and monocytes involves separate mechanism(s). (no Refs)

32. CHARACTERIZATION AND PROGNOSIS VALUE OF HUMAN AUTOLOGOUS ROSETTE FORMING CELLS (ARFC) IN THE CANCER PATIENTS (MEETING ABSTRACT)

Rucheton M, Cupissol D, Longhi B, Favier F, Rey A, Favier C, Esteve C, Serrou B

Department of Chemo-Immunotherapy, Centre Paul Lamarque, Montpellier, France

Fed Proc; 41(3):810 1982

Human ARFC have been described at length by our group. Purification of peripheral blood lymphocytes capable of forming autologous rosettes can be performed with satisfactory yield and enrichment by centrifugation on a percoll cushion. Purified ARFC express HTLA, possess Fc receptor for IgM but not for IgG and are OKT4 positive. ARFC support only weak ADCC (antibody dependent cellular cytotoxicity) and NK (natural killer) activity but are responsible for autologous and allogenic MLC (mixed leukocyte killer), responding strongly to phytohemagglutinin and weakly to pokeweed mitogen and Con A (Concanavalin A). They demonstrate no suppressor activity after Con A stimulation and are JRA negative. Cytochemical and electron microscopic characterization suggest that ARFC form a homogenous cell subset. A clinical study including 50 malignant melanoma patients and 50 breast cancer patients was undertaken to evaluate the prognostic value of ARFC. The results show that 20% or less ARFC in peripheral blood samples represents an evolutive status. Variation of ARFC levels in malignant melanoma patients paralleled variations in beta-2-microglobulin. Simultaneous increase of both parameters correlated with clinical aggravation in 90% of cases. ARFC below 20% in breast cancer patients preceded advancing metastatic disease in 42% of cases. (no Refs)

33. ALTERATION IN IMMUNE RESPONSE IN PATIENTS RECEIVING HUMAN FIBROBLAST INTERFERON (IFN-B) (MEETING ABSTRACT)

Matheson DS, McPherson TA, Tan YH, Green B

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Fed Proc; 41(3):406 1982

The efficacy of IFN as a therapeutic agent in the treatment of human malignancies is controversial. Animal experiments have suggested that the mechanism of action of IFN is indirect and involves an alteration in host immune response. Natural killer (NK) cells are thought to have protective activity against malignant cells and unlike other immune functions which are generally inhibited by IFN, NK activity is augmented in vitro. The immune response was studied in three patients who received partially purified IFN-beta (5x10(7) units/mg protein). Peripheral blood lymphocytes were assayed at various times after the intravenous infusion. Previous in vitro data indicated that the effect of the IFN-beta was to inhibit T cell mitogenesis and enhance B cell mitogenesis and NK function. In vivo, T cell mitogenesis was inhibited by IFN-beta but surprisingly so was the B cell mitogenesis and NK activity. The onset of the depression was noticeable within one hour and recovery began approximately 8-10 hours later. NK activity was decreased secondary, to the IFN-beta infusion and added exogenous IFN-beta given in vitro to these cells further inhibited the level of NK. Possible explanations of these phenomena include altered trafficking of the NK cells out of the circulating lymphocyte pool or excessive dosage of IFN-beta which can have an inhibitory effect on NK activity. (no Refs)

34. SUPPRESSION OF NATURAL KILLER CELL ACTIVITY BY ADHERENT CELLS FROM CANCER PATIENTS (MEETING ABSTRACT)

Uchida A, Colot M, Micksche M

University of Vienna, Vienna, Austria

Proc Am Assoc Cancer Res; 23:1061 1982

In cancer patients after surgery blood adherent cells suppressed natural killer (NK) activity against K562 cells determined in a 4-hr chromium release assay of normal lymphocytes and were responsible for the postoperative depression of NK activity, as is the case with malignant pleural effusions. The mere addition of adherent cells to cytotoxicity assays did not inhibit NK activity. Twenty-four hr contact of NK cells and 10% adherent cells resulted in suppression of NK activity. Adherent cells also suppressed the enhancement of NK activity by interferon. These results suggest that adherent cells inhibit the maintenance and development, but not effector phase, of NK cells. After prolonged contact with adherent cells, most NK cells changed their form from irregular motile one to round resting one and lost their active motility. Thid could be one mechanism of NK suppression since the motility of NK cells is a critical step of NK-cell-mediated cytolysis. This was confirmed by using a new agarose microdroplet assay in which NK cells migrated from agarose droplets toward target cells in medium and killed them. Treatment of adherent cells with monensin or cytochalasin B inhibited their suppressor function, suggesting that adherent cells actively move, make contacts with NK cells, and secrete some substance into NK cells. An immunotherapeutic agent OK-432, a streptococcal preparation, reduced the suppressor activity of adherent cells both in vivo and in vitro. Possibly, OK-432 leads adherent cells to some level of activation. (no Refs)

35. REGULATION OF NATURAL KILLER CELL (NKC) ACTIVITIES IN CANCER PATIENTS AND NONCANCEROUS INDIVIDUALS BY RECOMBINANT INTERFERON-ALPHA-CLONE-A (R-IFN-ALPHA-A) (MEETING ABSTRACT)

Lotzova E, Savary CA, Gutterman GU, Hersh EM, Quesada JR, Pestka S

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Proc Am Assoc Cancer Res; 23:1058 1982

Since r-IFN-alpha A has therapeutic potential in cancer, we have studied its effect on NKCs-the cells implicated as one of the components of tumor immunity. NKC activity of peripheral blood was measured against K-562 tumor cell line in a 3 hr 51Cr release assay. We observed significant augmentation of NKC cytotoxicity in 11 noncancerous individuals after treatment with r-IFN-alpha-A, independent of whether the effector cells were preincubated with r-IFN-alpha-A, or r-IFN-alpha-A was added directly to the cultures. NKC augmentation and its degree was dependent on the concentration of r-IFN-alpha-A employed; cytotoxicity was augmented with concentration of 10(3) units/ml, but was significantly less, or not potentiated with 10(2) or 10 units/ml. Kinetic studies indicated that the augmentation of NKC cytotoxicity was prompt, since the effect was observed as early as 10 min after incubation of effector cells with r-IFN-alpha-A. Despite the augmentation of lytic activity of NKCs, the NKC-tumor cell-binding properties were not changed by r-IFN-alpha-A. NKC cytotoxicity of 9 cancer patients, with various diagnosis, was also modulated by r-IFN-alpha-A. Four to 8 hr after a single im injection of 50-68 x 10(6) units of r-IFN-alpha-A, a decrease of NKC cytotoxicity was observed in all patients. The subsequent NKC modulation depended on the NKC phenotype of cancer patients, ie, 6 of 6 low NKC responders were potentiated 24 hr after a single r-IFN-alpha-A injection, whereas 3 of 3 high NKC responders were not significantly augmented. These data indicate that r-IFN-alpha-A is a potent NKC stimulatant. (no Refs)

36. WOUND HEALING IN THE IMMUNOSUPPRESSED HOST.

Kottra CJ
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AORN J; 35(6):1142,1144-1145,1148 1982

Biological aspects of immunologic compromise are reviewed with respect to planning a specialized nursing approach to wound care. The components of the immune system that contribute to wound healing include the inflammatory response, phagocytosis, and humoral and cell-mediated immunity. Immunosuppressive conditions that delay wound healing include immunologic disease, age-related deficiencies, conditions or diseases such as malnutrition and cancer, and immunosuppressive drugs, including steroids, antiinflammatory agents, and cytotoxic drugs. Cancers such as multiple myeloma, chronic lymphocytic leukemia, and lymphosarcoma result in deficiencies in circulating immunoglobins which are exacerbated by antineoplastic drug therapy, irradiation, poor nutrition, and general debilitation due to disease. Cytotoxic drugs, including actinomycin D, 5-fluorouracil, colchicine, and vinblastine sulfate, frequently inhibit the healing of surgical wounds. Wound healing in the immunosuppressed patient requires that the injured area remain a favorable environment for inflammatory, fibroblast, and endothelial cell activities. Nursing care which involves increasing local blood flow, providing adequate nutrition, assessing immunologic support measures, and meticulous wound care can promote wound healing in patients from high-risk populations. (12 Refs)

37. HUMORAL IMMUNOREGULATION IN CANCER PATIENTS.

Urushizaki I, Ishitani K, Ishida N, Herberman RB
Dept. Internal Medicine, Sapporo Medical COll., Sapporo, Japan
Excerpta Med Int Congr Ser; 576:127-146 1981

The effect of serum factors from gastric cancer patients on lymphocyte responsiveness to phytohemagglutinin (PHA) was tested before and after immunochemotherapy with Lentinan (5 mg iv, 2-3x/wk) and Ftorafur (FT-207) (800 mg/day). Cancer sera reduced PHA response of normal lymphocytes, with more suppression with advancing disease. Fractionation of cancer sera by diethylaminoethyl (DEAE) column chromatography yielded nine fractions. Fractions 5 and 6 gave specific PHA response suppression from cancerous sera only. Purification of these showed an acidic alpha-2 macroglobulin component. This component gave significant PHA response suppression at doses greater than 50 ug/ml, and enhanced tumor growth in mice. After immunochemotherapy five responding patients had a reduction of serum immunosuppressive activity, while 10 nonresponders did not. On gel electrophoresis the five responders had a band which might correspond to the LA band of mice, which was not seen in sera from the nonresponders. DEAE fractionation of sera from the responders showed a new band in fraction 4. Purification of this material yielded three peaks, the heaviest of which enhanced PHA responsiveness of normal lymphocytes, and significantly inhibited tumor growth in mice. (13 Refs)

38. THE CANCER PATIENT.

Smith JA, Whitaker AJ, Wise CC, Fox M
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Clin Res Rev; 1:33-35 1981

The role of the immune response in neoplastic development is discussed, particularly in cancer patients undergoing surgery. During surgery, the patient is subject to a number of stimuli, all of which reduce cell-mediated immunity and theoretically increase the risk of cancer growth and dissemination Stimulation of immune defense mechanisms by sepsis, aprotonin and injection of vaccine or BCG is discussed; nutritional support was also found to be important in improving nitrogen balance and maintaining muscle protein. (no Refs)

39. IN VIVO NONSPECIFIC MACROPHAGE CHEMOTAXIS IN CANCER PATIENTS AND ITS CORRELATION WITH EXTENT OF DISEASE, REGIONAL LYMPH NODE STATUS, AND DISEASE-FREE SURVIVAL.

Israel L, Samak R, Edelstein R, Amouroux J, Battesti JP, De Saint Florent G
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Cancer Res; 42(6):2489-2494 1982

We have used a test to evaluate macrophage migration in vivo, derived from the technique of Rebuck. The test is based on counting the absolute number of macrophages that migrate into an inflammatory site determined by a standardized superficial skin abrasion. It was applied to the study of macrophage migration in cancer patients in different clinical situations. Macrophage migration was virtually abolished in patients with metastatic cancer as compared to healthy controls. In patients with resectable breast and lung tumors, the test performed preoperatively correlated closely with lymph node status as determined by pathological examination after operation. Patients without lymph node involvement showed a significantly stronger response than did controls, whereas those with lymph node involvement had a diminished or even an abolished response. Distinctive subgroups were characterized among patients both with and without lymph node involvement on the basis of their macrophage response, and these subgroups proved to have distinctly different prognoses, particularly the patients without lymph node involvement with a poor macrophage response who had an unusually poor prognosis. It is concluded that this test shows potential for predicting the prognosis among categories of patients hitherto considered as homogeneous, although further evaluation in larger numbers of patients is necessary. (Author abstract) (22 Refs)

40. STUDIES ON IMMUNITY IN PATIENTS WITH UROGENITAL CANCERS. REPORT 2. EFFECT OF ABNORMAL SERUM PROTEINS ON NONSPECIFIC CELLULAR IMMUNITY.

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Nippon Hinyokika Gakkai Zasshi; 72(8):1078-1091 1981

Subfraction levels of prealbumin (PA), alpha1-antitrypsin (a1-AT), alpha1-acidglycoprotein (a1-AG), ceruloplasmin (Cp) and haptoglobin (Hp) were measured in the serum of 66 patients with bladder carcinoma, 16 with renal cell carcinoma, 21 with pelvic and ureteric carcinoma, 19 with prostatic carcinoma, 5 with testicular tumor, 15 with other malignancies, 22 with benign prostatic hypertrophy, and 15 with no malignancy.

Effects of the serum proteins on nonspecific cellular immunity was studied. Skin response to 2-4 dinitrochlorobenzene (DNCB) and purified protein derivative (PPD) and lymphocyte blastogenesis induced by phytohemagglutinin (PHA) and pokeweed mitogen (PWM) were used as indicators of immune response. Alpha1-globulins were significantly increased in patients with metastatic renal carcinoma, pelvic and ureteric carcinoma, or other malignant tumors, and the increases were directly related to the stage of the cancer. High levels of IgG and IgM were observed in the patients with renal cancer but not in other patients. Patients with urinary tract cancers had elevated levels of PA, a1-AG, a1-AT, Cp, and Hp; a1-AT was significantly increased in patients with advanced cancers. Decreased response to PPD was associated with significant decreases in PA and increases in a1-AT, Cp, and Hp. Except for PA and a1-AG, no other serum proteins were associated with changes in DNCB responses. After the addition of autologous serum, PHA-induced blastogenic response was positively correlated with levels of serum PA and negatively correlated with levels of serum a1-AG, a1-AT, and Cp. PWM-induced response was not correlated to levels of serum glycoproteins. The patient's lymphocyte reactivity index was negatively correlated to a1-AT and Cp levels, suggesting suppression of T lymphocyte function by these glycoproteins. (27 Refs) (In JPN)

41. CELL-MEDIATED IMMUNITY IN TUMOR PATIENTS SUBJECTED TO SURGERY.

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Orv Hetil; 123(10):595-597 1982

The cell-mediated immunity was monitored in 147 tumor patients before and for more than 1 yr after surgery. Carcinomas of the stomach, small and large intestines were diagnosed in 105 patients, breast cancer in 32, other tumors in 10. The tests included the determination of the absolute lymphocyte count, absolute T-cell count, intracutaneous skin tests, rosette tests, and the leukocyte migration inhibition test. Fifty-four blood donors served as controls. The tests performed in the breast cancer patients before and 2 wk after surgery showed no significant differences from the corresponding control values. The leukocyte migration inhibition test showed no significant differences between the patients with colorectal carcinomas and the controls. Good migration inhibition was observed in the gastric cancer patients regardless of stage, and a decreasing tendency was observed only in the patients with nonresectable tumors or with distant metastases. Tumor resection caused no significant changes in the immune status of the 147 patients. The immunological tests proved to be unsuitable for the early detection of tumor recurrence. (27 Refs) (In HUN)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

42. SENSITIVITY OF ADENOVIRUS-TRANSFORMED CELL LINES OF DIFFERENT TUMORIGENICITY TO KILLING BY SYNGENEIC NATURAL KILLER CELLS (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:949 1982

In this study, the tumorigenic potentials of six adenovirus-transformed LIS cell lines were studied in syngeneic rats. The cells used are well characterized as to the content and expression of the adenovirus genome. The in vivo tumorigenic potential of these individual cell lines in LIS rats varied from nontumorigenicity in immunosuppressed newborn animals to high tumorigenicity in untreated newborn and weanling rats. This different capacity to induce tumors does not correlate with a number of in vitro properties of these cell lines, such as growth saturation density, decreased doubling time, increased fibrinolytic activity or anchorage independent growth. Similarly, the ability of these cell lines to elicit the cytolytic T cell response in syngeneic LIS rats also does not universally correlate with their tumorigenic potential. When the capacity to induce tumors in vivo, however, was compared with the sensitivity of these transformed cell lines to in vitro killing by natural killer (NK) cells in syngeneic lymphoid cell preparations, an inverse relation was found between these two parameters. In parallel experiments no significant differences were detected in the sensitivity of these cell lines to in vitro killing with syngeneic secondary cytolytic T cells. (no Refs)

43. REGULATION OF THE EXPRESSION OF ADOPTIVE TUMOR REJECTION IMMUNITY BY RECIPIENT CYCLOPHOSPHAMIDE-SENSITIVE CELLS.

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Cancer Res; 42(6):2211-2215 1982

Peritoneal exudate T-cells from rats immune to 13762A rat mammary tumor conferred specific tumor rejection immunity on normal recipients. The efficiency of systemic adoptive transfer of tumor rejection immunity with immune peritoneal exudate T-cells was improved by cyclophosphamide (CY) pretreatment of recipients. Optimal potential was obtained with a dose of 50 or 100 mg CY per kg body wt given the day before transfer. CY pretreatment of recipients was effective 1 to 3 days prior to transfer. The CY-potentiating effect was lost with longer intervals between CY administration and transfer, indicating recipient recovery. CY pretreatment enabled recipients to reject greater numbers (100 times) of tumor cells and inhibited tumor challenge established before systemic adoptive transfer. The CY-induced potentiation of systemic transfer of tumor immunity was reversed by iv-administered normal spleen. We concluded that CY-sensitive host regulatory cells restricted the expression of adoptive tumor rejection immunity. Control of the activity of these regulatory cells allows increased efficacy of effector T-lymphocytes in this system. (Author abstract) (21 Refs)

44. SELECTIVE DEPLETION OF NK CELL ACTIVITY IN VIVO AND ITS EFFECT ON THE GROWTH OF NK-SENSITIVE AND NK-RESISTANT TUMOR CELL VARIANTS.

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Int J Cancer; 29(5):567-574 1982

Intravenous injection of rabbit anti-asialo-GM serum, an antiserum previously shown to eliminate splenic natural killer in CBA, DBA/2, and BALB/c nu/nu mice. The effect on NK activity was selective. The role of NK cells in controlling tumor cell growth was investigated using an NK-sensitive and an NK-resistant subline of the murine lymphoma L5178Y. The possibility that the effects observed were caused by binding of the injected antibodies to the tumor cells was minimized by: (1) using a clone of tumor cells that lacks chemically detectable asialo-GM, and (2) pretreating animals with anti-asialo-GM rather that administering antiserum and tumor cells concurrently. These studies provided compelling evidence that NK cells could play an active role in controlling tumor growth. Selective depletion of NK activity by injection of anti-asialo-GM serum is a method which would be generally applicable to studying the role of NK cells in disease processes. (28 Refs)

45. THE MECHANISM OF IMMUNOSUPPRESSION IN TUMOR-BEARING MICE: DIFFERENT SUSCEPTIBILITY OF VARIOUS IMMUNE RESPONSES TO IMMUNOSUPPRESSION AND MACROPHAGE SERIES AS TARGETS FOR IMMUNOSUPPRESSION.

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Fukuoka Igaku Zasshi; 72(12):687-702 1981

Immunosuppression was investigated in thymic lymphoma (EL-4)-bearing C57BL/6 mice immunized with chicken red blood cells (CRBC). Corynebacterium parvum was used as macrophage activating agent. After a primary immunization with CRBC, production of antibody, cell mediated cytotoxicity (CMC), and delayed type footpad reaction (DFR) were suppressed; soon thereafter the reactions, except for DFR, were restored despite enlargement of the tumor. After a secondary immunization, only DFR was suppressed. Before immunization, the introduction of serum taken from the tumor-bearing mice suppressed production of antibody slightly but strongly suppressed CMC and DFR; after immunization, only DFR was suppressed. The effect of transfer of spleen cells taken from tumor-bearing mice with secondary immunization on DFR was similar to that of transfer of spleen cells taken from similarly immunized normal mice. No DFR was induced with spleen cells taken from primary immunized tumor-bearing mice. The administration of C parvum restored the production of antibody, CMC, and DFR. In the secondary immunized tumor-bearing mice, administration of C parvum restored DFR but had no effect on production of antibody and CMC. DFR was restored with C parvum treatment in the tumor-bearing mice adoptively transferred with spleen cells taken from immunized DFR positive mice. Only the group of spleen cells from which cells adhering to the glass petri dish had been removed lost the ability to restore the suppressed immune reaction. In vitro experiments showed that accessory cell function of adherent cells was impaired in the tumor-bearing mice and treatment with C parvum restored the function. When serum obtained from the tumor-bearing mice was fractionated by Sephadex G-200, the fraction containing molecules with relatively high mol wt exhibited immune suppression ability. The results suggest that immune suppression may be the result of lowered accessory cell function of macrophages and suppression of macrophages as the secondary cell in FDR. C parvum seems to restore both functions by stimulating macrophages. (58 Refs) (In JPN)

46. RESISTANCE TO L1210 MOUSE LEUKEMIA CELLS IN MODERATELY PROTEIN-MALNOURISHED BALB/C MICE TREATED IN VIVO WITH THYMOSIN FRACTION V.

Petro TM, Watson RR
Dept. Foods and Nutrition, Purdue Univ., West Lafayette, IN, 47907
Cancer Res; 42(6):2139-2145 1982

Moderate protein malnutrition retarded the ip proliferation of L1210 mouse leukemia cells in BALB/c mice. The increased resistance against leukemia cell growth in protein-malnourished mice was correlated with increased in vitro mitogenic responsiveness of spleen lymphocytes to phytohemagglutinin and increased levels of serum corticosterone but could not be correlated with altered development of splenic lymphocyte-mediated cytotoxicity. The increased resistance against leukemia cells in well-fed mice treated with thymosin alone could not be correlated with an increase in any of these parameters. Treatment with Thymosine Fraction V further increased the resistance of protein-malnourished mice to ip leukemia cell growth. The increased resistance of these mice to tumor cell growth was correlated with increased splenic lymphocyte mitogenic responsiveness to phytohemagglutinin, elevated serum corticosterone levels, and a slight increase in lymphocyte-mediated cytotoxicity 14 days after tumor challenge. For 7 days after the last treatment, protein-malnourished mice had reduced serum corticosterone levels. Nevertheless, the serum corticosterone levels were still higher than normal in these mice. (Author abstract) (34 Refs)

47. DIFFERENCES IN ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY AGAINST TUMOR CELLS IN IN VITRO DIFFERENTIATING MONONUCLEAR PHAGOCYTES FROM BONE MARROWS OF NORMAL AND INFLAMED MICE.

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Cell Immunol; 68(1):53-63 1982

Mononuclear phagocytes, differentiated in vitro from bone marrow cells of mice inflamed in vivo with either Corynebacterium parvum or thioglycollate, expressed a higher activity in antibody-dependent cellular cytotoxicity (ADCC) against tumor cells, than those of normal mice. A good correlation between the cytolytic activity and chemiluminescence activity of the different mononuclear phagocyte populations was observed. The ADCC activity of BMDMP from normal mice was inhibited by exogenous prostaglandin E2 (PGE2) to a higher extent than that of BMDMP of inflamed mice. When the three BMDMP populations were cultured in the presence of aspirin (without exogenously added PGE2), the ADCC was significantly increased. The three populations gave identical high values. This suggests that the differential ADCC activity of BMDMP from normal and inflamed mice is due to their differential response to endogenous prostaglandins. PGE2 showed also a differential effect on the mononuclear phagocyte-forming capacity of bone marrow macrophage precursor cells from normal and inflamed mice. Bone marrow precursor cells from inflamed mice showed a higher resistance to the suppressive effect of PGE2 (10(-5) M) on mononuclear phagocyte-forming capacity than those of normal mice which were totally suppressed. It is concluded that the observed differential properties of the three bone marrow-derived mononuclear phagocyte populations originate at the level of bone marrow precursor cells and that, therefore, the similar functional differences observed in inflammation-induced peritoneal macrophage populations, observed by our and other groups, stem at least partly from differences at the level of bone marrow precursor cells. (Author abstract) (31 Refs)

48. CELL-MEDIATED IMMUNITY AGAINST CONNECTIVE TISSUE IN EXPERIMENTAL PULMONARY FIBROSIS.

Carvajal RE, Gonzalez R, Vargas-A F, Selman M
(c/o Selman) Departamento de Patologia Experimental, Instituto Nacional de la Nutricion, Mexico 22 D.F., Mexico
Lung; 160(3):131-140 1982

The behavior of lymphocytes obtained from 9-wk-old male CD1 outbred mice with bleomycin (BLE: total dose 275 mg/kg)-induced pulmonary fibrosis in the presence of pulmonary connective tissue (CT) extract and/or BLE was analyzed in vitro. The cellular immune response was assayed in intervals for a total of 7 wk after initiation of the process, in order to examine the time at which the lymphoid system becomes reactive to CT. Main changes during the first 2 wk consisted of necrosis of the epithelial components of the alveolar capillary structures, hyperplasia of Type II pneumonocytes, and the progressive accumulation of inflammatory and immunocompetent cells in the alveolar space and interstitium. Abnormal deposits of intercellular substances, mainly collagen and elastin, were observed from wk 3 of the experiments. The production of migrant inhibitory factor (MIF) by cells from BLE-treated and control mice over 7 wk in the presence of CT or BLE extract is presented. Lymphocytes from mice with experimentally induced fibrosis showed a small but nonsignificant response to CT extract after wk 3. The response was significant (50-60% inhibition) in the final wk, but total inhibition was never observed. The possibility that BLE impaired MIF production in the lymphocytes in vitro was tested by measuring the response of cells from fibrotic animals to CT extract in the presence of BLE in wk 6 and 7. No inhibition of the response was observed under these conditions. Significant stimulation of DNA synthesis in the presence of the extract was observed, while BLE had the effect of reducing thymidine uptake below control levels. According to the results it was not possible to determine whether a cellular immune response was induced by BLE. (41 Refs)

49. AN ADOPTIVE CELL TRANSFER SYSTEM FOR THE EVALUATION OF IMMUNITY TO HERPES SIMPLEX VIRUS IN MICE.

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Clin Exp Immunol; 48(2):307-314 1982

Lymphocytes adoptively transferred from syngeneic immune donors protect mice against challenge with Herpes simplex virus Type 1. Normal mice require transfer of 3 x 10(7) spleen cells for protection. Sublethal irradiation (450 rad) decreases the number required five-fold. Lymphocytes from non-immune donors do not protect, and hyperimmunization does not enhance the protection efficiency of donors. The viral LD50 varies through a range 10(5)-fold during the period of recovery from this amount of radiation, but over the same period there is little variation in the number of cells required for protection. Nor is there much variation in this number between strains of mice naturally susceptible (CBA) and resistant (C57) to this virus. We conclude that natural resistance operates at a level of virus handling prior to operation of the lymphocyte system, perhaps at the generation of interferon. As few as 1.3 x 10(6) immune T lymphocytes can protect against challenge provided that they are transferred together with normal spleen cells. We conclude that primed lymphocytes act in cooperation with non-immune cells. (Author abstract) (18 Refs)

50. EVIDENCE FOR TWO FUNCTIONALLY DISTINCT CROSS-REACTIVE TUMOR ANTIGENS ASSOCIATED WITH ULTRAVIOLET LIGHT AND CHEMICALLY INDUCED TUMORS.

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Transplantation; 33(4):352-360 1982

Experiments were conducted to determine the distribution and function of common tumor antigens shared by UV light-, benz[a]pyrene (BP)-, and methylcholanthrene (MCA)-induced tumors. When lymph node cells were removed from UV, BP, or MCA tumor-immune mice and held in tissue culture for 4 days, a population of cytotoxic T lymphocytes (CTLs) emerged that were capable of lysing a battery of different tumor targets. These CTLs displayed crossreactive in vivo activity in Winn-type assays. These CTLs recognized tumor-associated antigens (TAAs) common to both UV and chemically induced tumors. These common TAAs were incapable of eliciting cross-protective tumor immunity when tumor immunizations and challenges were made entirely in vivo. The state of cross-protective immunity within hyperimmune mice is directed toward shared tumor-associated transplantation antigens (TA-TAs). These particular determinants are related to the induction etiology of the tumor. Previous reports have suggested that the suppressor T lymphocytes (Ts cells) present in UV-treated animals possess functional specificity for the common TATAs expressed by UV tumors. We believe that UV-induced Ts cells recognize the common TAAs shared by UV and MCA tumors. Collectively, these data define at least two different classes of common tumor antigens expressed by UV and chemically induced tumors. These antigenic determinants are functionally defined as the TATAs and the common TAAs. The shared TATA function in vivo as rejection antigens and are restricted to tumors induced by the same carcinogenic agent. In contrast, the common TAAs shared by UV and chemically induced tumors are not only recognized by CTLs but more importantly function as immunoregulatory determinants. The importance of these common tumor antigens in host-tumor interactions is discussed. (32 Refs)

51. APPARENT LACK OF IMMUNOGENICITY OF ESTROGEN INDUCED MOUSE LEYDIG CELL TUMORS (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:924 1982

Evaluating 4 in vivo indicators of immune response, we attempted to demonstrate immunogenic properties in transplantable malignant Leydig cell tumors (LCT) induced in BALB/c mice by chronic estrogen administration. Growing LCT failed to elicit the production either of the lymphokine MIF by splenocytes or of circulating antibodies detectable by indirect immunofluorescence. Delayed type hypersensitivity was evaluated in animals 'sensitized' by growing tumor explants. Three to 6 weeks after tumor excision, 10(6) viable cells or frozen whole cell equivalents were injected sc in one foot pad and 2 days later the increase in popliteal node weight on that side determined. Node hypertrophy of 'immunized' animals in numerous experiments employing many mice was no greater than that in the naive controls, and no evidence could be obtained to suggest the stimulation of 'suppressor cell activity' during 'sensitization'. Finally, pretransplantation treatment of recipients with 400 r total body x-ray failed to increase the growth rate of 4 different tumor lines. Although 14 transfer lines from 9 primary LCT were investigated, several with each methodology, all studies yielded negative results while each method successfully demonstrated an appropriate response to at least 2 of 3 transplantable tumors of other cell types that were weakly immunogenic to BALB/c mice due to viral associated or histocompatability antigens. These findings, plus the absence of recognizable virions in 5 lines on electron microscopic examination, argue against the participation of an 'expressed' virus in the genesis of LCT. The lack of immunogenicity is consistent with the indefinite persistence of microscopic foci of viable, though dormant, malignant cells in estrogen dependent LCT that have undergone complete clinical regression following hormone withdrawal. (no Refs)

52. CORYNEBACTERIUM PARVUM (CP) IMMUNOTHERAPY OF THE L5178Y CELL TUMOR DORMANT STATE IN DBA/2 MICE (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:968 1982

The L5178Y cell tumor dormant state in DBA/2 mice is characterized by immunocompetence of the host and persistence of low numbers of tumor cells in the peritoneal cavity, making it ideal for evaluating immunotherapeutic regimens. CP was used for active non-specific immunotherapy and a CP double inoculation protocol developed which maximized cellular influx into the peritoneal cavity and cytolytic activity of the adherent peritoneal cells (AD-PEC). A peritoneal lavage was performed to enumerate the tumor burden in tumor dormant mice and to isolate tumor cells for use as targets in subsequent cytolytic assays. Mice were inoculated with 350ug CP on day 3 and day 10 after peritoneal lavage and were killed on day 19 at which time the PEC were assayed for endogenous tumor burden and AD-PEC cytolytic activity. Forty-seven percent of mice which received CP therapy were without detectable tumor cells, whereas 100% of PBS (phosphate-buffered saline)-treated controls contained tumor cells. The AD-PEC from mice that had no detectable tumor cells produced generally greater cytolytic activity in vitro when tested against their own previously isolated tumor cells than the AD-PEC from mice which remained tumor dormant. Small numbers of tumor cells were isolated from some CP treated mice that had a degree of AD-PEC cytolytic activity comparable to that in the PEC of tumor negative mice, thus supporting the validity of the negative tumor cell isolations from CP treated mice. The effector AD-PEC were characterized as macrophages by adherence to plastic, morphology, and resistance to anti-Thy 1.2 + C'. (no Refs)

53. ALLOIMMUNIZATION-INDUCED SYNGENEIC ANTITUMOR IMMUNITY IN BALB/C MICE (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:1010 1982

To test whether alloimmunization with H-2 or/and non-H-2 different normal tissues may increase the immunity to syngeneic tumors, groups of BALB/c (H-2d) mice were immunized with a series of allogeneic lymphoid cells and then challenged IP with syngeneic lymphoma cells. The outgrowth of otherwise lethal doses of the Moloney virus-induced lymphoma YC8 and of its clones was inhibited in BALB/c mice immune to DBA/2 (H-2d), C3Hf (H-2k), C3H.SW (H-2b), C3H.OH (H-2O2) and to B10 background tissues but not in mice immunized to A/He, BALB.K (H-2k) or BALB.B (H-2b) normal tissue. Anti-YC8 effect was also induced by immunizing BALB/c recipients with a pool of 5 different allogeneic cells which included C3Hf, C57BL/6J (H-2b), N:NIH (H-2q), B10.M (H-2f), and DBA/2 lymphoid cells. No growth inhibition of other BALB/c lymphomas induced by Moloney virus (LSTRA) or urethan (UR-1) was evident in alloimmune mice. This effect was abrogated by anti-Thy 1.2 plus C' treatment of alloimmune peritoneal exudate cells. In addition, nu/nu BALB/c mice were unable to develop resistance to YC8 outgrowth after alloimmunization. The results of this study show that: 1) syngeneic growth of a lymphoma can be prevented by alloimmunization with normal cells; 2) the cross-reaction involved non-H-2 antigens; 3) the phenomenon appeared to be mediated by T cells. (no Refs)

54. INTERLEUKIN 2 ACTIVITY IN FIBROSARCOMA-BEARING HOSTS (MEETING ABSTRACT)

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Fed Proc; 41(3):318 1982

It has been established in our laboratory that there is a decrease in Interleukin 2 (IL-2) activity with increasing tumor burden. A 28-day kinetic study using spleen cells from BALB/c mice injected with methylcholanthrene-induced fibrosarcoma cells revealed a 59% drop in IL-2 activity between Days 8 and 10 of tumor development and no IL-2 detectable at Day 28. The addition of purified IL-2 preparations to standard proliferation assays induced normal host spleen cells to a higher level of blastogenesis and reconstituted hyporeactive tumor-bearing host (TBH) spleen cells to normal basal levels. When added to a mixed lymphocyte reaction (MRL), IL-2 enhanced the response of both normal host spleen cells and purified T cell preparations (suppressor T cells removed) to stimulator B cells. TBH whole spleen cell MLR reactivity was slightly suppressed, whereas the TBH T cell response was increased over basal levels with IL-2 addition. Antiserum studies, using anti-Thy 1.2, anti-Lyt 1.2 and anti-Lyt 2.2 to deplete specific populations, showed that helper T cells present in TBH spleens were capable of IL-2 production in the absence of tumor-induced suppressor T cells. Absorption studies were done using conditioned medium or purified IL-2 to identify the receptor population in both normal and TBH. (no Refs)

55. RESISTANCE TO L1210 MOUSE LEUKEMIA CELLS IN MODERATELY PROTEIN MALNOURISHED BALB/C MICE TREATED IN VIVO WITH THYMOSIN FRACTION (MEETING ABSTRACT)

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Fed Proc; 41(3):357 1982

Female weanling BALB/c mice were fed a 20% casein control (C) or 4% casein low protein (LP) diet. The LP diet or treatment with bovine, a series of injections with thymosin fraction V (BTF5) totalling 700 ug, independently rendered mice more resistant to intraperitoneal (IP) growth of 10(7) L1210 mouse leukemia cell growth. In mice fed LP, reduced growth of the leukemia L1210 was correlated with increased mitogenic responsiveness of spleen lymphocytes to phytohemagglutinin (PHA) and increased levels of serum corticosterone. The growth in vitro of L1210 cells was significantly inhibited by corticosterone. Treatment of mice fed LP with BTF5 increased the resistance to L1210 cell growth above that in mice fed LP and injected IP with saline. For 7 days after the last BTF5 treatment mice fed LP had reduced serum corticosterone levels. However, these levels were still higher than those of mice fed C diet. The increased resistance to leukemia cell growth in mice fed LP treated with BTF5 was correlated with increased splenic lymphocyte responsiveness to PHA and an increase in development of cell mediated cytotoxicity 14 days after leukemia cell challenge. These data suggest that the increased resistance of moderately protein malnourished mice against cancer cell growth may be partially the result of increased in vivo corticosterone levels. (no Refs)

56. IN VIVO INHIBITION OF TUMOR GROWTH BY SPLEEN CELLS FROM TUMOR BEARING MICE AFTER IN VITRO EDUCATION (MEETING ABSTRACT)

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Fed Proc; 41(3):406 1982

Spleen cells from BALB/c mice bearing a progressively growing transplantable sarcoma induced by methylcholanthrene (CE-2) do not react specifically with the tumor, nor are they able to inhibit its growth. These cells can be educated to be efficiently active against the tumor. Twenty-five x 10(6) spleen cells and 10(6) Mitomycin C treated tumor cells were co-cultured in a total volume of 20 ml of RPMI 1640 medium supplemented with 10% fetal bovine serum and 5 x 10(-5) M 2-Mercaptoethanol for 6 days. The surviving cells were placed in culture for another 5 days in the same conditions, with the addition, however, of 10% lectin-free T cell Growth Factor. These cells were now able to inhibit the growth of a 100% lethal dose of CE-2 in a Winn type assay at a lymphocyte:tumor cell ratio of 5:1. This protection was not reduced by removal of Lyt 2+ lymphocytes. By contrast, lymphocytes cultured without stimulating CE-2 target cells or in the presence of mitogens were found to be ineffective even at 600:1. In vitro studies showed that these effector cells did release interferon gamma, but did not exhibit significant cytotoxicity to CE-2 nor to NK-sensitive target cells. (no Refs)

57. MECHANISM OF DEPRESSED NATURAL KILLER (NK) ACTIVITY IN P815 TUMOR BEARING MICE (MEETING ABSTRACT)

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Fed Proc; 41(3):602 1982

The NK activity of DBA/2 spleen cells declines to undetectable levels 12 days after the initiation of an P815 ascites tumor. Tumors were induced with an intraperitoneal injection of 10(7) P815 tumor cells. An active suppression of NK cell activity by either suppressor humoral factors or by suppressor cells could not be detected therefore the loss of spleen NK activity in tumor bearing mice was considered to represent a genuine lack of NK cells. To test this hypothesis lethally x-irradiated syngeneic mice were reconstituted with spleen or bone marrow cells from tumor bearing mice. The transplanted cells were able to develop significant levels of NK activity and cell fractionation studies showed that this activity was mediated by NK cells. Therefore, the loss of NK activity in tumor bearing mice is not due to a lack of NK precursor stem cells, or the presence or suppressor cells or factors. It is proposed that the NK precursor stem present in tumor bearing mouse spleen or bone marrow have an impaired differentiation ability in the pathway to active cytotoxic NK cells. (no Refs)

58. NATURAL CYTOTOXIC ACTIVITY OF EARLY INFLAMMATORY PERITONEAL EXUDATE CELLS IN MICE (MEETING ABSTRACT)

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Fed Proc; 41(3):803 1982

Early inflammatory peritoneal exudate (EIPE) cells recovered from mice 18 hours after ip injection of thioglycollate are capable of killing radiolabelled tumor targets in an overnight 51Cr release assay. When EIPE cells are reacted against a panel of tumors, the most sensitive targets fall into the natural killer (NK)-sensitive category, with YAC-1 being the most lysable tumor (levels of specific 51Cr release up to 40%). The cytotoxic effect, however, seems to be distinct from NK cell activity in that: a) it is virtually absent at 4 hours, b) does not parallel splenic NK levels, c) occurs independently of age and strain of donor mice and d) is detectable at attacker-target ratios lower than those required for NK splenic expression. Furthermore EIPE cells are largely adherent to nylon wool column, but not to plastic surfaces. It is suggested therefore that cytotoxic cells distinct from NK lymphocytes, promonocytes and macrophages can be found in the EIPE which is mostly made up of polymorphonuclear neutrophils. (no Refs)

59. A LACK OF NATURAL KILLER CELL ACTIVITY IN DOMESTIC CATS (MEETING ABSTRACT)

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Fed Proc; 41(3):802 1982

Natural killer (NK) cells have been identified in a wide variety of species. After preliminary studies failed to detect NK cell activity in domestic cats we studied NK and lymphocyte mediated antibody-dependent cellular cytotoxicity (ADCC) in cats in detail. Peripheral blood lymphocytes (PBL) and spleen cells from cats of various breeds were evaluated for cytotoxicity against cultured YAC-1, RL male 1, G1-TC, FL-74, Raji, and EL-4 tumor cell lines and against antibody-coated Raji and chicken erythrocytes. Short (4 hours) and long (18 hours) term 51Cr release cytotoxicity assays were used and spleen cells from rats were assayed concurrently as controls. Aliquots of effector cells were incubated with the interferon inducer polyinosinic-polycytidylic acid (poly I:C), which augments NK activity in other species. Target binding assays were performed with three tumor cell lines. Although cat lymphocytes bound to tumor cells they did not manifest spontaneous NK activity against any of the tumor cell lines with either short or long assays and poly I:C did not induce NK activity. ADCC against Raji tumor cells was absent but ADCC against antibody-coated chicken erythrocytes was present. It is concluded that domestic cats as a species lack NK cell activity and ADCC against tumor targets and that the deficiency resides in the lytic phase of the phenomenon. (no Refs)

60. RELATIONSHIP OF IN VITRO LEUKOCYTE REACTIVITY TO THE GROWTH AND SPONTANEOUS REGRESSION OF SWINE MELANOMA (MEETING ABSTRACT)

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Sinclair Comparative Medicine Research Farm and University Missouri, School of Medicine Columbia, MO, 65201
Fed Proc; 41(3):415 1982

The objective of this study was to determine if in vitro leukocyte reactivity could be correlated with the in vivo growth and regression of swine melanoma. Longitudinal studies were performed using a visual microcytotoxicity assay and cryopreserved swine peripheral blood leukocytes. Comparison of longitudinal leukocyte reactivity with in vivo tumor volumes indicated that swine with regressing melanomas exhibited increased leukocyte reactivity during tumor regression. Swine with relatively small tumor volumes exhibited patterns of leukocyte reactivity which paralleled the patterns of in vivo tumor growth and regression. However, swine with large tumor volumes often demonstrated increased leukocyte reactivity at the time of maximum in vivo tumor volume. Histopathologic analyses revealed that increases in tumor volumes were frequently a result of host inflammatory cells, particularly pigment-laden macrophages (PLM), infiltrating the tumors. Thus at the time of maximum tumor volumes, the melanomas already were undergoing regression. Initial studies indicate that the primary effector cell in the in vitro leukocyte assay is a T lymphocyte. These studies indicate that the spontaneous regression of swine melanoma is associated with immunologic events. (no Refs)

61. GROWTH AND SPONTANEOUS REGRESSION OF SWINE MELANOMA: RELATIONSHIP OF IN VITRO LEUKOCYTE REACTIVITY.

Berkelhammer J, Ensign BM, Hook RR, Hecker CJ, Smith GD, Oxenhandler RW
Veterinary Clinical Sciences, Sch. Veterinary Medicine, Louisiana State Univ., Baton Rouge, LA, 70803
JNCI; 68(3):461-468 1982

A visual microcytotoxicity technique was used to evaluate the leukocyte reactivity of melanoma swine against allogeneic swine melanoma target cells. Peripheral blood leukocytes, which had been collected and cryopreserved in liquid nitrogen at various times during in vivo tumor growth and regression, were thawed and tested on the same day. Comparison of longitudinal leukocyte reactivity with in vivo tumor volume indicated that swine with regressing melanomas exhibited increased leukocyte reactivity during tumor regression. Swine with maximum tumor volumes less than 30,000 m3 exhibited patterns of leukocyte reactivity that paralleled the patterns of in vivo tumor growth and regression. However, swine with maximum tumor volumes greater than 30,000 m3 demonstrated increased in vitro leukocyte reactivity at the time of maximum in vivo tumor volume. Histopathologic analyses revealed that increases in tumor volume were frequently a result of host inflammatory cells, particularly pigment-laden macrophages, infiltrating the tumors. Thus at the time of maximum tumor volume, malignant melanocytes were proportionately decreasing in number while pigment-laden macrophages were proportionately increasing. These studies provide additional evidence that the spontaneous tumor cell regression of swine melanoma is associated with immunologic events and that assays of leukocyte reactivity are useful in vitro correlates of host antitumor immunity. (Author abstract) (18 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

62. METABOLIC REQUIREMENTS OF INTERFERON-ENHANCED HUMAN NATURAL CYTOTOXICITY (MEETING ABSTRACT)

Bishop GA, Schwartz SA

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Fed Proc; 41(3):804 1982

We examined the biochemical requirements of interferon (IF) enhanced human natural killer (NK) activity, using as effector cells peripheral lymphocytes enriched for NK effectors by density gradient centrifugation. Cells were incubated with or without human alpha-IF, prior to or following treatment with various metabolic inhibitors. NK activity was quantitated by release of 51Cr from K562 target cells. Augmentation of NK activity was initiated in a rapid, temperature-independent manner, requiring only a 10-15 min exposure to IF, and occurred at either 4 or 37C. Significantly enhanced activity was observed by 2 h of effector-target interaction. Augmentation was inhibited by prior treatment of NK cells with actinomycin D (AD), but treatment with AD after 1 h of IF treatment did not inhibit the IF-mediated increase in cytotoxicity, suggesting that the RNA species required are synthesized within 1 h of cell-IF contact. Protein synthesis is required following cell-IF contact, as shown by the ability of emetine and puromycin treatments to abrogate increased NK cell activity. Preliminary results indicate that Tunicamycin, a glycosylation inhibitor, has no effect on spontaneous or IF-enhanced NK activity. IF-induced enhancement was unaffected by incubation of effectors with mitomycin C either before or after IF treatment. This indicates that IF acts primarily upon a population of preexisting cells. (no Refs)

63. STUDIES ON THE ANTITUMOR ACTIVITY OF INTERFERON II. EFFECT OF INTERFERON ON HUMAN ACUTE LYMPHOBLASTIC CELL LINES GROWN IN HAMSTERS.

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Second Dept. Internal Medicine, Okayama Univ. Medical Sch., Okayama, Japan
Okayama Igakkai Zasshi; 93(9/10):851-859 1981

B-cell and T-cell human leukemic cell lines, BALL-1 and TALL-1, were transplanted into newborn hamsters immunosuppressed with rabbit anti-hamster lymphocyte serum. The growth inhibitory effect of interferon (IF) was tested by ip administration in these tumor-bearing animals. The following results were obtained: (1) TALL-1 transplanted ip was inhibited much more than BALL-1 transplanted sc. The life span of hamsters transplanted with TALL-1 was also prolonged. These findings coincided with the results of in vitro sensitivity of these two cell lines to IF. (2) The antiproliferative effect of a combination of cyclophosphamide and IF to BALL-1 was greatly enhanced compared with when either agent was used alone. (3) The combined use of L-asparaginase and IF was similarly more inhibitory to TALL-1 than either agent alone. It seems that the growth of residual tumor cells after chemotherapy can be effectively inhibited by IF. In using IF for cancer chemotherapy, therefore, it would be advisable to combine chemotherapeutic agents with IF. (Author abstract) (29 Refs) (In JPN)

64. MODULATION OF NATURAL KILLER CELL-MEDIATED CYTOTOXICITY BY PARTIALLY PURIFIED AND CLONED INTERFERON-ALPHA.

Lotzova E, Savary CA, Gutterman JU, Hersh EM
Dept. Clinical Immunology and Biological Therapy, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(6):2480-2488 1982

We have studied peripheral blood of 35 normal individuals, 28 solid-cancer patients, and 14 leukemic patients for natural killer (NK) cell cytotoxicity to K-562 and CEM tumor cells in a 51Cr release cytotoxicity assay. We have found that both normal individuals and solid-cancer patients could be grouped into high (NK-HR), medium (NK-MR), and low (NK-LR) NK cell responder categories with regard to their degree of NK cell activities. However, in general, NK-HRs were found to be prevalent in normal donor population and NK-LRs in cancer patients. Leukemic patients always exhibited the NK-LR status. The difference between NK-HRs and NK-MRs appeared to be due to the relative decrease in number of active NK cells. In contrast, the NK-LR status could not be contributed to decrease of NK cells because of the dichotomy in NK cell dose-response patterns of NK-LRs versus those of NK-HRs and NK-MRs. Eighteen cancer patients undergoing interferon-alpha (IFN-alpha) therapy (3 x 10(6) units, im, daily) were also tested for NK cell activities after single or multiple IFN-alpha injections. There was a highly significant and consistent increase in NK cell cytotoxicity of patients with the NK-LR and NK-MR phenotypes following one injection of IFN-alpha. In contrast to the NK-LR and NK-MR group of patients, most patients displaying the NK-HR phenotype failed to show any NK cell augmentation following any number of IFN-alpha injections (up to 119). We have also tested NK cell activities of cancer patients undergoing treatment with low (3 x 10(6) units) and high (36 x 10(6) and 50 x 10(6) units) doses of clone A of recombinant IFN-alpha (IFN-alpha rA). In these studies, all patients receiving the lower doses of IFN-alpha rA and three of five patients receiving the higher doses of IFN-alpha rA displayed augmented Nk cell activity 24 hr after a single im injection. Analysis of patients receiving the low dose of IFN-alpha rA in a single-cell assay suggested that this agent did not modulate tumor-NK cell-binding properties but augmented significantly Nk cell cytotoxicity and killing of already-bound tumor targets. (Author abstract) (50 Refs)

65. INDUCTION AND AUGMENTATION OF MITOGEN-INDUCED IMMUNE INTERFERON PRODUCTION IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES BY NALPHA-DESACETYLTHYMOSIN ALPHA1.

Svedersky LP, Hui A, May L, McKay P, Stebbing N

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Eur J Immunol; 12(3):244-247 1982

Treatment of human peripheral blood lymphocytes with cloned Nalpha-desacetylthymosin alpha1 induced interferon production. The kinetics is similar to that of mitogen-induced interferon induction. Nalpha-desacetylthymosin alpha1, in combination with mitogen, augments the amount of interferon produced. This interferon is immune interferon (IFN-gamma) as determined by sensitivity to pH 2, lack of neutralization by antibodies to IFN-alpha or IFN-beta and absence of activity on MDBK cells. Although the mechanism of induction of IFN-gamma by Nalpha-desacetylthymosin alpha1 is unclear, this compound is not mitogenic at concentrations causing IFN-gamma production. These results indicate that thymic factors may also participate in the regulation of IFN-gamma production. (Author abstract) (25 Refs)

66. THE HUMAN IL-2 INDUCED KILLER CELL PHENOMENON: LYSIS OF NK RESISTANT FRESH SOLID TUMOR CELLS BY IL-2-ACTIVATED PBL (MEETING ABSTRACT)

Grimm EA, Mazumber A, Rosenberg SA

National Cancer Institute, Bethesda, MD, 20205

Fed Proc; 41(3):957 1982

Activation of cancer patients' peripheral blood lymphocytes (PBL) in culture for 7 days in partially purified lectin-free human T-cell growth factor containing IL-2 yielded cytotoxic effector cells capable to lysing fresh autologous tumor cells (melanoma, sarcoma, and carcinoma). Lysis of autologous tumor cells was positive in 14/16 cases, as measured in a 4-hr 51Cr release assay. In 5 cancer patients whose fresh PBL did not lyse fresh tumor, lysis was found in all cases after activation. Under identical assay conditions 13/13 fresh solid tumor cells were found to be resistant to natural killer (NK) activity found in the fresh PBL of 17 normal individuals (224/239 tests). Kinetic studies showed that culture for at least 2 days in TCGF was required for IL-2 induced killer cells (IKC) to develop. Lysis was not unique to autologous tumor cells, since all fresh or cultured tumor cells were lysed by IKC, though in most cases fresh PBL were not lysed. Generation of IKC was also possible using PBL of normals, showing that the IKC phenomenon is not restricted to cancer patients. While the IKC was found to resemble a T cell by serologic and adherence studies, its rapid kinetics of development along with absence of requirements for antigenic stimulus suggests that it is not a classic CTL or NK, but rather a distinct cell type. (no Refs)

67. AFFINITY PURIFICATION OF HUMAN CANCER ASSOCIATED INHIBITORS OF MONOCYTE FUNCTION USING MONOCLONAL ANTIBODIES TO A MURINE RETROVIRAL PROTEIN (MEETING ABSTRACT)

Cianciolo GJ, Snyderman R
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Fed Proc; 41(3):845 1982

Macrophages (M) can destroy tumor cells and may participate in defense against neoplasia. In mice, the retrovirus protein P15E suppresses M accumulation to inflammatory stimuli. Recently we found that human cancerous effusions contain proteins which inhibit the change in morphology of monocytes from round to a triangular 'motile' shape in response to chemoattractants (polarization). The inhibitors in cancerous effusions bound to monoclonal antibodies against murine P15E. To characterize these inhibitors, we coupled monoclonal anti-P15E to Sepharose 4B. This affinity column bound the polarization inhibitory activity (PIA) contained in 4 cancerous effusions tested. Affinity purified material inhibited polarization to the chemotactic peptide FMLP (formylmethionylleucylphenylalanine) by up to 74%. The potency of this material was evidenced by its ability to half maximally inhibit at concentrations of ca 0.3 ng/ml. Affinity column purification produced an increase in specific activity of greater than 100,000 fold. Column retentates of 3 non-cancerous effusions contained no activity at concentrations of up to 100 ng/ml. Fractionation of the affinity purified PIA by HPLC (high pressure liquid chromatography) revealed 3 peaks of activity greater than or equal to 200,000, approx 100,000 and approx 20,000 daltons. This elution profile was similar to that obtained by HPLC fractionation of whole cancerous effusion, the activities of which were also bound by monoclonal anti-P15E. Thus human cancerous effusions contain 3 potent inhibitors of monocyte function differing in size but antigenically related to P15E. (no Refs)

68. ACTIVATED T-CELLS INHIBIT HUMAN MYELOMA IGE PRODUCTION (MEETING ABSTRACT)

Hassner A, Saxon A
University of California at Los Angeles, Los Angeles, CA, 90024
Fed Proc; 41(3):825 1982

Modulation of IgE synthesis from a human myeloma cell line (E266) was accomplished with activated T-cells from normal donors. Maximal inhibitory effect on IgE production was observed when the T-cells were incubated with U266 in the presence of 10 ug/ml of Con-A (concanavalin A). Similar inhibition was observed after preincubation of T-cells for 24 or 48 hours with Con-A and subsequent culture with U266 in the absence of Con-A. The decrease in IgE measured was not due to inhibition of preformed IgE secretion as shown by experiments with Cycloheximide. Supernatants of activated T-cells also suppressed IgE production suggesting the presence of inhibitory material(s) secreted by activated T-cells. Activation of T-cells by mixed lymphocyte culture had an effect similar to Con-A in respect to IgE production. Generation of the suppressive activity on T-cells is likely a non-specific process. This was further supported by the ability of activated T-cells to suppress production of IgG and IgA by human lymphoid cell lines. Preincubation of T-cells with Con-A and IgE did not alter their ability to suppress the production of IgE by U266 in spite of the fact that patients with high serum levels of IgE have been shown to have a loss of circulating T suppressor cells for IgE. Utilizing this reproducible system for human IgE synthesis, the molecular basis for down regulation of IgE from an active secreting cell can be investigated. (no Refs)

69. INHIBITION OF MURINE MIXED LYMPHOCYTE REACTION (MLR) AND CELL-MEDIATED CYTOTOXICITY (CMC) BY EXTRACTS OF FRESH HUMAN TUMOR (MEETING ABSTRACT)

Davidson DD, Sugarbaker PA, Roth JA
National Cancer Institute, Bethesda, MD, 20205
Fed Proc; 41(3):819 1982

We investigated the role of human tumor-derived immunoregulatory factors (IRF) in the suppression of murine in vitro cell-mediated immune systems. IRF was extracted from fresh colon carcinomas or liposarcoma using 3M KCl. These extracts have previously been shown to suppress in vitro human immune responses. Colon adenocarcinoma IRF inhibited PHA (phytohemagglutinin)-stimulated murine splenocyte 3H-Tdr (thymidine) uptake in a dose-dependent manner. To further investigate in vitro immunosuppression a (C57BL/6 x A/J) Fl anti B10.BR mixed lymphocyte reaction was developed. Optimal 3H-Tdr incorporation was on day 4 with 1 x 10(5) responders and 2 x 10(5) irradiated stimulators. Addition of IRF caused a 56% inhibition of this response. Maximal inhibition (94%) on day 1 diminished during the first 6 days of MLR culture. Induction of cell-mediated cytotoxicity (C57BL/6 x A/J F1 vs B10.D2) was significantly inhibited by addition of IRF during in vitro sensitization. Release of 51Cr from H-2d P-815 targets was decreased to spontaneous release levels at effector: target (E:T) ratio 20:1 when IRF was present during sensitization. At this E:T ratio cells sensitized in the presence of muscle 3M KCl extract or medium caused 71% and 60% 51Cr release, respectively. These results indicate that human IRF extracts have immunosuppressive properties for murine as well as human cell-mediated immune responses. (no Refs)

70. IDENTIFICATION AND CHARACTERIZATION OF A MURINE IMMUNO-SUPPRESSIVE FACTOR FROM A UV-INDUCED MELANOMA K-1735 (MEETING ABSTRACT)

Putnam JB, Roth JA
Surgery Branch, National Cancer Institute, Bethesda, MD, 20205
Fed Proc; 41(3):818 1982

An immunosuppressive factor derived from a UV-induced murine melanoma was identified and characterized. The primary melanoma and three of its metastases were grown in vivo and harvested in early passages (4-10). Tumors were extracted in 3M KCl for varying times and the extracts tested for suppresion of in vitro 3H-thymidine (3H-Tdr) incorporation by mitogen stimulated splenocytes. Extracts of the primary tumor and all metastases suppressed stimulated 3H-Tdr uptake (26-63% suppression). The effects of the factor on mitogen stimulated splenocytes were entirely reversible by washing after a 24 hour incubation with factor. The extracts did not effect cell viability. Normal muscle and liver extracts showed no suppressive activity. The specific activity of the factor was directly proportional to the length of extraction (up to 7 days). The immunosuppressive activity of the tumor extracts was heat stable, yet labile to acid, base and 2-mercaptoethanol. Activity was reduced by treatment with proteolytic enzymes, and neuraminidase but lipase had no effect. In conclusion, a primary murine melanoma and its metastases produce an immunosuppressive glycoprotein which may be important in the mechanism of tumor-associated immunosuppression. (no Refs)

71. CELLULAR INTERACTIONS IN THE GENERATION OF CELL-MEDIATED CYTOTOXICITY TO SYNGENEIC TUMORS IN VITRO (MEETING ABSTRACT)

Lynch DH, Gurish MF, Daynes RA

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Fed Proc; 41(3):409 1982

Repeated ultraviolet (UV) irradiation of mice can result in their inability to mount an effective anti-tumor immune response and is associated with a population of T-suppressor (Ts) cells. However, UV-induced Ts cells may not be the only mechanism by which tumor susceptibility is mediated. Using in vitro methods we have evaluated the effects of UV-exposure on the modification of 1) tumor antigen processing and presentation, 2) T-cell priming and 3) cytotoxic T lymphocyte (CTL) maturation. Draining lymph nodes (DLN) from tumor-immunized mice were found to contain a population of radiation resistant, Thy 1-, Ia+ antigen presenting cells (APC). APC from both normal and UV-irradiated mice were compared and exhibited equivalent functional capabilities. DLN from both normal and UV-irradiated tumor-immunized mice were also found to contain primed T cells which differentiate into anti-tumor CTL with similar kinetic profiles. Further, subsequent to functional inactivation of Ts cells, spleens of UV-irradiated tumor-bearing mice could be demonstrated to contain a population of cells which impart partial protection against tumor growth in vivo. Thus, normal and UV-irradiated mice appear capable of responding similarly in the afferent phases of immune responses to syngeneic tumor antigens, and suggests that UV-Ts cells mediate their regulatory effects at a late stage in the generation of effective anti-tumor immune responses. (no Refs)

72. CELLULAR INTERACTIONS IN VITRO IN A PRIMARY ANTI-TUMOR RESPONSE.

Levy JP, Gomard E, Wibier-Franqui J, Herberman RB, Chang KS, Aoki T, Hashimoto Y

Laboratoire d'Immunologie et de Virologie des Tumeurs, Hopital Cochin, Paris, France

Excerpta Med Int Congr Ser; 576:268-281 1981

Factors affecting generation of mouse spleen cytotoxic T lymphocytes (CTL) against tumor cells carrying a virus-induced antigen closely related to the serologically defined FMR system (anti-FMR CTL) were investigated. Cytotoxicity was determined by 51Cr release. In vitro generation of primary anti-FMR CTL appeared to require the presence of a radioresistant, adherent, phagocytic, Thy 1-2-negative cell, probably a macrophage. These macrophages interacted with T cells because of Ia specificities. CTL activity was directed by the tumor cell H-2 specificity. This requirement for macrophages could be replaced by interleukin 2 (IL2), suggesting that macrophages may trigger IL2 production by presenting an Ia+ antigen to an anti-FMR helper T cell. Further work showed that Thy1-2 (+) primed helper T cells in the presence of normal macrophages triggered anti-FMR CTL from normal thymocytes. Lentinan (1 mg/kg days-7 to-2) increased CTL production, but not consistently. Other work suggests that Lentinan may increase the sensitivity of precursor CTL to IL2. (19 Refs)

73. IMMUNOREGULATORY FACTORS DERIVED FROM HUMAN TUMORS. I. IMMUNOLOGIC AND BIOCHEMICAL CHARACTERIZATION OF FACTORS THAT SUPPRESS LYMPHOCYTE PROLIFERATIVE AND CYTOTOXIC RESPONSES IN VITRO.

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J Immunol; 128(5):1955-1962 1982

Immunoregulatory factors (IRF) that suppress normal human peripheral blood mononuclear cell (PBM) function can be extracted from a variety of fresh human tumors. Three molar potassium chloride extracts of 18 fresh human tumor specimens, including sarcomas, melanomas, and lung carcinomas, markedly inhibited 3H-leucine and 3H-thymidine incorporation by PBM in response to mitogens (phytohemagglutinin, concanavalin A, Pokeweed mitogen) and pooled mitomycin C-treated allogeneic PBM. Induction of human allospecific cell-mediated cytotoxicity was also inhibited. Extracts of human normal and fetal tissues were not inhibitory. IRF could be extracted from either cultured tumor cells or from spent culture media from a melanoma cell line grown in chemically defined, serum-free media, demonstrating IRF is a tumor product. Although IRF were extracted from three histologically distinct tumors, the extracts had several common characteristics. Preincubation of PBM with IRF followed by washing prevented inhibition of lectin-stimulated proliferation. Inhibiton was greatest when IRF were added immediately to cultures. IRF were heat-stable and resisted inactivation by papain, chymotrypsin, protease, and lipase; they could be partially inactivated by trypsin treatment. Inhibitory activity was removed from extracts by lentil lectin affinity chromatography and recovered by elution with 3% alpha-methyl-D-mannoside indicating the active moiety contained a carbohydrate. Inhibitory activity was also abolished by extreme acid or base conditions and treatment with 2-mercaptoethanol. These results demonstrate that factors produced by human tumors suppress a variety of cell-mediated immune responses. Factors from histologically different tumors possess similar biochemical and immunobiologic characteristics. (Author abstract) (46 Refs)

74. EFFECTS OF LYMPHOKINES ON TUMOR CELLS.

D'Silva HB, Yoshida T

Dept. Pathology, Univ. Connecticut Health Center, Farmington, CT, 06032

The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

The direct and indirect effects of lymphokines, soluble mediators of cell-mediated immunity, on tumor cells are discussed. Topics presented include: macrophage and leukocyte migration inhibition factors, tumor cell migration inhibition factor, macrophage activating factor and specific macrophage arming factor, interferon, lymphotoxins, and in vivo effects of lymphokines on tumors. (191 Refs)

75. SUPPRESSION OF THE CYTOTOXIC RESPONSE TO MAJOR HISTOCOMPATIBILITY ANTIGENS (MHC) BY A SOLUBLE PRODUCT OF SUPPRESSOR CELLS (MEETING ABSTRACT)

Terpenning M, Zighelboim J
Department of Microbiology and Immunology, University of California at Los Angeles School of Medicine, Los Angeles, CA, 90024
Proc Am Assoc Cancer Res; 23:1030 1982

Disordered regulation of the immune response has been suggested to contribute to the development of certain malignancies. We have previously shown that antigen specific splenic suppressor cells are generated by the intravenous administration of Corynebacterium parvum during alloimmunization of C57BL/6 (H-2b) with P815 (H-2d) mastocytoma cells. We now present evidence that a soluble product of a subset of these cells mediates suppression of cell mediated cytotoxicity (CMC). These cells, when cultured in the presence of specific alloantigen, release a factor (SF-CTL) which strongly inhibits primary but not secondary in vitro sensitization of B6 splenocytes to H-2d targets. The activity of SF-CTL is antigen dependent and genetically unrestricted. The producer cell is plastic and nylon wool nonadherent and has low sensitivity to anti-Thy sera and complement. Preliminary characterization has shown that SF-CTL 1) has an approximate molecular weight of 80,000 daltons, 2) does not bear constant region determinants of immunoglobulin, 3) is inhibitory only when added during the initial 24 hours of culture, and 4) is not directly cytotoxic to P815. We conclude that SF-CTL represents an antigen dependent product of a subset of suppressor cells which inhibits via intercellular communication the afferent phase of primary allogeneic sensitization. (no Refs)

76. RESTORATION OF ALLOGENEIC RESPONSIVENESS OF LYMPHOCYTES FROM CYCLOSPORIN A-TREATED ANIMALS WITH INTERLEUKIN 2.

Wang BS, Heacock EH, Zheng CX, Tilney NL, Mannick JA
Dept. Chemotherapy Res., Medical Res. Div., American Cyanamid Co., Lederle Laboratories, Pearl River, NY, 10965
Transplantation; 33(4):454-456 1982

The possibility that a defect at the helper cell level results in the inability to generate allocytotoxicity in cyclosporin A (Cy A)-treated mice was examined. The results indicated that the failure of alloreactivity resulted from the deletion or impairment of helper cells capable of producing interleukin 2 following Cy A treatment. Mechanisms by which Cy A may act on helper cells are discussed. (29 Refs)

77. INTERLEUKIN 1, A POTENTIAL REGULATOR OF FIBROBLAST PROLIFERATION.

Schmidt JA, Mizel SB, Cohen D, Green I
Lab. Immunology, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
J Immunol; 128(5):2177-2182 1982

Secondary mixed lymphocyte reaction (MLR) supernatants contain factors that stimulate fibroblast proliferation in vitro. Biochemical analysis of secondary MLR supernatants using gel filtration chromatography and isoelectrofocusing (IEF) demonstrated that the fibroblast proliferation factors have apparent mol wt of 75,000 and 13,000 and isoelectric points (pI) of 6.8 to 7.2, 5.8 to 6.2, and 5.2 to 5.4, values similar to those previously reported for human interleukin 1 (IL 1). To further explore the relationship between the MLR-derived fibroblast proliferation factors and IL 1, the following experiments were performed. First, the fractions obtained from gel filtration and IEF were assayed for both thymocyte proliferation activity, a measure of IL 1 activity, and fibroblast proliferation activity, and superimposable activity profiles were obtained. Second, to confirm that the observed thymocyte proliferation activity was in fact due to IL 1 and not interleukin 2 (IL 2) or novel factors, the IEF fractions contained peak thymocyte and fibroblast proliferation activity (ie, fractions having pI of 6.8, 6.0, and 5.3, respectively) were demonstrated to stimulate IL 2 production by a murine T lymphoma line, a specific measure of IL 1 activity. Third, IL 1 and the fibroblast proliferation factors were co-purified through a three-step, 200-plus-fold purification protocol consisting of ammonium sulfate precipitation, gel filtration chromatography, and IEF. Fourth partially purified human IL 1 made in another laboratory and highly purified murine IL 1, but not human and murine IL 2, stimulated fibroblast proliferation. These results demonstrate that the fibroblast proliferation factors found in secondary MLR supernatants have several functional and biochemical properties in common with human IL 1. These findings raise the possibility that IL 1 may regulate fibroblast proliferation and that the local production of IL 1 by infiltrating mononuclear cells may contribute to the fibrosis observed in chronic inflammatory disease states. (Author abstract) (55 Refs)

78. ANTIGEN PRESENTATION TO PRIMED T CELLS BY ADHERENT IA+ TUMOR CELL LINES (MEETING ABSTRACT)

Cohen DA, Smith LA, Kaplan AM
Medical College of Virginia, Richmond, VA, 23298
Fed Proc; 41(3):299 1982

We have previously described the isolation of several Ia+ adherent cell lines (P388AD) cloned from the P388 leukemia which possess many morphological and functional similarities with dendritic cells of the spleen. P388AD has been shown to induce strong syngeneic (SMLR) and allogeneic (AMLR) mixed leukocyte reactions in vitro, whereas several nonadherent Ia+ clones (P388NA) isolated from the same parent tumor are unable to induce the T-cell proliferative responses. We now present evidence that the stimulatory capacity of P388AD compared to P388NA correlates with the ability of the AD but not the NA clones to secrete interleukin-1. P388AD but not P388NA clones present a soluble antigen, turkey gamma globulin (TGG) to primed DBA/2 spleen cells and P388AD-TNP induce the production of T-cells cytotoxic to TNP-H2d targets. When P388AD are pulsed in vitro with TGG and then cultured with TGG-primed, nylon wool-enriched T-cells, P388AD elicits an antigen-specific proliferative response, whereas P388NA does not. P388AD retains its antigen-presenting function even after removal of endogenous antigen-presenting cells from the nylon-wool enriched TGG primed T-cells with anti-Iad plus complement, suggesting that P388AD does not artifactually present TGG by shedding antigen to Ia+ macrophages. (no Refs)

79. CAROTENE AND NATURAL KILLER CELL ACTIVITY (MEETING ABSTRACT)

Leslie CA, Dubey DP
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Fed Proc; 41(3):331 1982

There exists some epidemiologic evidence to show that dietary carotene may reduce cancer risk. In the studies reported here the possibility was explored that carotene may alter some immune function. Human lymphocytes were incubated for 1 or 3 hours with carotene (alpha or beta at 1uM and .01uM), vehicle (0.1ul/ml) or medium alone. After washing, the cells were incubated with 51Cr labeled tumor cells at 3 effector target (E/T) ratios and specific Cr release calculated. Vehicle alone slightly depressed Cr release. There was no evidence that carotene or vehicle increased total cell death. While there was a slight enhancement of Cr release by alpha carotene treated cells, the effect of beta carotene was more pronounced. At an E/T ratio of 50, beta carotene treated cells released 28% Cr after 1 hour incubation and 40% after 3 hours. The 3 hour values for untreated, vehicle and alpha carotene treated cells were 28%, 23% and 24% respectively. These experiments suggest that beta carotene is increasing Cr release by a mechanism other than protection from effects of vehicle and may be directly increasing the cytotoxicity of natural killer cells. (no Refs)

80. IMMUNOLOGICAL CHARACTERISTICS OF ANTI-TUMOR POLYSACCHARIDES, LENTINAN AND ITS ANALOGUES, AS IMMUNE ADJUVANTS.

Akiyama Y, Kashima S, Hayami T, Izawa M, Mitsugi K, Hamuro J, Kumagi K, Herberman RB, Aoki T, Urushizaki I, Chang KS, Ishida N, Tsubura E, Levy JP

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Excerpta Med Int Congr Ser; 576:227-243 1981

Immunological and biological characteristics of Lentinan (L) are reviewed. The main characteristics of L may be listed as follows: (1) does not enhance macrophage phagocytic activity; (2) does not induce suppressor macrophages; (3) is not directly cytotoxic; (4) does not work after po administration; (5) works via a T-cell-dependent pathway. L appears to function as an immune adjuvant by causing increased production of interleukin 1 (IL1: lymphocyte-activating factor). This increased production results in enhanced maturation of immunocompetent T cells reactive to Interleukin 2 and natural killer cell inducing factor, and hence increased production of effector cytotoxic T lymphocytes and natural killer cells. Lentinan also appears to enhance macrophage reactivity to macrophage activating factor, resulting in increased numbers of effector macrophages. (16 Refs)

81. ANTI-TUMOR EFFECT OF LENTINAN IN THE MOUSE SYSTEM.

Yamada Y, Kubota T, Hanatani Y, Matsumoto S, Kumai K, Ishibiki K, Abe O, Chang KS, Urushizaki I, Hosokawa M

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Excerpta Med Int Congr Ser; 576:219-226 1981

Lentinan (L: 1 mg/kg/day for 5 consecutive days) was assessed for its effect on growth of the transplantable 20-methylcholanthrene-induced KKN-1 fibrosarcoma in nude (nu/nu) and heterogeneic nude mice on a BALB/c genetic background (nu/+). The ratio of the estimated tumor wt of the treated group to that of the untreated group (T/C) was used to measure effectiveness. Preliminary work showed that the tumor wt could be estimated accurately (p less than 0.01) from measurements. Tumor wt doubling time was 2.5 days for the nu/nu mice and 3.7 days for the nu/+ mice. After treatment with L on days 1-5 the T/C ratio decreased gradually for the nu/+ mice, reaching 57.3% at day 21, but remained the same for nu/nu mice (103.1%) at day 21. Administration of L to nu/+ animals on days-5 to-1, 1 to 5, and 6 to 10 gave T/C ratios of 103.8%, 57.3%, and 80.1%, respectively. The findings in the nu/nu mice appear to indicate the importance of the thymus and T cells in the action of L. (11 Refs)

82. ANTI-TUMOR EFFECT OF POLYSACCHARIDE LENTINAN ON TRANSPLANTED ASCITES HEPATOMA-134 IN C3H/HE MICE.

Moriyama M, Miwa H, Orita K, Tsukagoshi S, Hosokawa M, Herberman RB, Urushizaki I, Ishida N, Levy JP

Dept. Surgery, Okayama Univ. Medical Sch., Okayama, Japan

Excerpta Med Int Congr Ser; 576:207-218 1981

The antitumor effect of Lentinan (L) against the MH134 ascites hepatoma in C3H/H3 mice, and its optimal dose and time of administration, were investigated. L was administered 10x ip. Tumor inhibition was estimated from tumor diameter. L was tested at 0.5, 1, 2, and 10 mg/kg, with doses of 1 and 2 mg/kg giving a significant (p less than 0.05) effect. L was then given at 1 mg/kg from days-10 to-1, 1 to 10, or 8 to 17. The third regimen gave the best results, a tumor proliferation-inhibition rate of 33%, indicating that L is most effective against established tumor. A combination of L with chemotherapy with mitomycin C, 5-fluorouracil, and cytosine arabinoside gave slightly better results than L alone; the chemotherapy alone had no effect. Antitumor activity of L in vitro was studied by the macrophage inhibition (MI) test. In untreated mice implanted with MH134, the activity of lymph nodes reached its max on day 6, and soon after the activity of spleen cells became positive. Then on day 14 the MI activity of both regional lymph nodes and spleen cells disappeared. In contrast, in the group given L, the activity of the regional lymph nodes followed the same course as in the untreated group, but the activity of the spleen cells remained positive even after day 14. L appears to be most effective when given at an early stage when the host's cellular immunity is decreasing. (12 Refs)

83. AUGMENTATION OF NATURAL KILLER (NK) CELL ACTIVITY BY LENTINAN.

Herberman RB, Nunn-Hargrove ME, Levy JP, Ishida N, Tsubura E, Chang KS, Gotoda E, Sendo F, Hashimoto Y

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Excerpta Med Int Congr Ser; 576:188-198 1981

Natural killer (NK) cell activity was determined by a 4 hr 51Cr release assay in CBA/J and BALB/c mice greater than 12 wk of age (when there is low NK activity) after ip treatment with 100 ug of Lentinan (L). L treatment resulted in a significant rise in NK activity, with higher levels in the CBA/J mice. In these mice NK activity showed a peak at day 1, was normal by day 3, rose again on day 7, and appeared to drop below normal at days 10 and 14. This inhibition has been reported for other NK-boosting agents. Interferon activity in CBA/J mice was elevated at day 1 of treatment, and returned to normal by day 3. In BALB/c mice, which did not react as strongly to L, the depression of NK activity late in the experiment was not seen; there appeared to be a secondary rise in activity. These mice showed the initial rise in interferon followed by a drop on day 3, but the secondary rise in NK activity was not accompanied by a rise in interferon. L may be a valuable immune modifier because of its activity and lack of toxicity. (20 Refs)

84. AUGMENTATION OF NATURAL CELL-MEDIATED CYTOTOXICITY BY ADMINISTRATION OF LENTINAN IN MICE.

Sendo F, Seiji K, Fuyama S, Watabe S, Arai S, Herberman RB, Hashimoto Y, Oaki T
Dept. Pathology, Yamagata Univ. Sch. Medicine, Zao, Iida, Yamagata, Japan
Excerpta Med Int Congr Ser; 576:178-187 1981

The effect of Lentinan (L) (2-5 mg/kg im for 3 consecutive days) on natural killer (NK) and natural cytotoxic (NC) activity was investigated in spleen cells of mice. NK activity was measured by 51Cr release, NC activity by 3H-uridine release of the tested in vitro cell lines. L increased NC activity of BALB/c cells against Meth A (methylcholanthrene-induced) fibrosarcoma. With cells from a radiation-induced lymphoma (RLmale1: RIL), L increased NK activity in 4/5 experiments, compared to the control group. This increase was less than the increase of NC activity seen with Meth A cells. In more limited experiments with cells of a Moloney murine leukemia virus induced lymphoma (YAC-1), L increased NK activity. In experiments in (C57BL/6 x BALB/c) F1 mice, there was no significant difference in NC cell activity (compared to controls) on Meth A cells or NK activity on RIL cells. Results suggest that it may be possible to augment natural cell-mediated cytotoxicity through non-interferon pathways, since L does not effect this route, and that this augmentation may vary with the strain of animal. (16 Refs)

85. STUDY ON RELATIONSHIP BETWEEN EFFECTS OF BCG ON TUMOR GROWTH AND HOSTS' IMMUNE RESPONSES.

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First Dept. Surgery, Faculty Medicine, Kyushu Univ., Fukuoka 812, Japan
Fukuoka Igaku Zasshi; 72(12):667-686 1981

The effect on the host immune response against methylcholanthrene-induced transplanted sarcoma cells by introduction of BCG and/or tumor-derived microsome as tumor antigen was examined in C57BL/6 mice. In untreated tumor carrying mice, anti-tumor-derived microsome antibody in the serum increased as the tumor grew, reaching a plateau at a tumor size of 6 x 10(3) cubic mm; thereafter no increase was seen even though tumor growth continued. Treatment with tumor-derived microsome alone had no effect on tumor growth. Treatment with BCG alone or in combination with microsome inhibited tumor growth. In the latter case, tumor growth inhibition depended upon the combination: 1 mg BCG + 1 mg microsome showed the strongest tumor growth inhibition, whereas the combination of 8 mg BCG and 10 mg microsome promoted tumor growth. Before tumor transplantation, the amount of antibody was significantly higher in the mice treated with 8 mg BCG and 10 mg microsome than in other groups. Both before and after tumor transplantation, the amount of serum immune complex was higher in the tumor growth promotion group than in other groups. Before tumor transplantation, cell mediated cytotoxicity (CMC) was higher in the tumor suppressed group; after tumor transplantation, as the tumor grew, CMC increased in the tumor promotion group but decreased in the tumor suppressed group. A similar pattern was seen with antibody-dependent cell-mediated cytotoxicity. Significantly strong delayed type footpad reaction (hypersensitivity, DTH) was seen in the tumor suppressed group compared to the control group and the tumor promotion group before tumor transplantation; all treated groups showed decreased DTH after tumor transplantation, especially the tumor suppressed group. Phytohemagglutinin (PHA) reaction was markedly low in the tumor promotion group, whereas no significant difference was seen in other pretreated groups compared to the control. The PHA reaction decreased in normal spleen cells that had been incubated in the culture medium taken from the spleen cell culture of the tumor promotion group. Such results suggest that when immunotherapy is used for clinical control of cancer, parameters such as BCG dose and body immune response reaction must be carefully considered. (144 Refs) (In JPN)

86. THE ANTITUMOR EFFECTS AND EFFECT ON CELL-MEDIATED IMMUNITY OF CORYNEBACTERIUM PARVUM.

Nakamura K
First Dept. Surgery, Okayama Univ. Medical Sch., Okayama, Japan
Okayama Igakkai Zasshi; 93(9/10):909-923 1981

The antitumor effects and influence on cell-mediated immunity of Corynebacterium parvum (C parvum) were studied using C3H/He mice and syngeneic mouse ascites hepatoma MH 134 tumor. With the administration of C parvum alone, a significant antitumor effect was obtained in the group given 0.4 mg per day ip for 5 consecutive days from the 5th day after transplanting 5 X 10(5) cells/0.1 ml of MH 134 tumor sc on the back. A significant antitumor effect was also obtained when C parvum was combined with MF chemotherapy (Mitomycin C 1 mg/kg, 5-Fluorouracil 25 mg/kg), in the group given MF ip on the 5th day and 0.4 mg/day of C parvum ip for 5 consecutive days from the 7th day after tumor transplantation. The cell-mediated immunity in these two groups was investigated by using the delayed type hypersensitivity (DTH) and macrophage migration inhibition factor (MIF activity). The results were: no decrease in DTH was shown compared with the tumor-bearing untreated group. MIF activity was marked compared with the tumor-bearing untreated group and tended to persist for a long period. From these findings, it was concluded that C parvum was an effective immunopotentiator which yielded an antitumor effect by restoring the cell-mediated immunity of the tumor bearing host. The effect seemed to be enhanced when used in combination with chemotherapy. (Author abstract) (47 Refs) (In JPN)

87. THE INHIBITORY EFFECT OF FLUPHENAZINE ON CELL-MEDIATED CYTOLYSIS OF TUMOUR CELLS (MEETING ABSTRACT)

Laing LP, Boegman RJ, Roder JC
Queen's University, Kingston, Ontario, Canada
Fed Proc; 41(3):802 1982

Fluphenazine (FP), a phenothiazine derivative, binds to calmodulin (CaM), rendering it biologically inactive, and secondarily interferes with the organization of microtubules. Various concentrations of FP were tested for their effect on the murine NK (natural killer) mediated lysis of YAC tumor cells. A marked inhibition of NK activity was observed after a 1 hr treatment of NK effector cells at 37 degrees with a concentration of 2.5 x 10-5M, a non-toxic dose. Conjugate formation between effectors and targets decreased from 16.5-4% following FP treatment. Similarly, CTL derived either from MLC, (mixed lymphocyte culture) or by Con A (concanavalin A) stimulation were inhibited in their abilities to kill P815 tumor targets after FP treatment. Tumoricidal activity by activated macrophages and ADCC (antibody dependent cellular cytotoxicity) effectors was also blocked. When 3T6 fibroblasts were treated with FP, followed by fixation and immunofluorescent staining with antitubulin, striking dose-dependent changes in cell morphology and microtubule distribution were detected. Since CaM may be involved in the calcium-dependent regulation of the cytoskeleton, it was important to try to reverse the inhibitory effect of FP. Upon addition of the Ca++ ionophore A23187 to the NK assay of FP-treated effectors, a restoration to normal levels of lysis was noted. These data suggest that the inhibitory effect of FP results from disruption of microtubules. (no Refs)

88. SUPPRESSION OF NATURAL KILLER (NK) CELL ACTIVITY BY 3-METHYLCHOLANTHRENE (MEETING ABSTRACT)

Lill PH, Gangemi JD
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Fed Proc; 41(3):331 1982

NK cell reactivity has been proposed as a mechanism for non-T cell surveillance against spontaneous tumors. Therefore, carcinogen-induced suppression of NK activity could potentially facilitate tumor growth. One mg of 3-methylcholanthrene (3-MC) was injected sc between the shoulder blades and NK cell activity was measured by Cr release from YAC cells in a 4 hour assay. One mg 3-MC was found to suppress NK reactivity by 30 to 60 per cent four and six days post injection. No depression was found 2 days post injection and levels of NK reactivity returned to normal by 8 days post 3-MC injection. No suppression of NK activity was detected when doses of 3-MC ranging from 0.05 mg to 0.4 mg were tested. No suppression of NK reactivity was seen when tested 6 weeks after 3-MC treatment. 3-MC did not affect Corynebacterium parvum-induced augmentation of NK cell reactivity when tested both 6 days and 6 weeks post-3-MC injection. Therefore, preliminary results do not indicate that suppression of NK activity is important in allowing carcinogen-induced tumors to grow progressively since suppression of NK reactivity is not a long lasting effect and reactivity would return to normal before the tumor began to grow. In addition, lower doses of 3-MC are carcinogenic but do not suppress NK cell activity. If NK cell activity were effective against cells at an early time after transformation suppression of NK cell activity might play a role. (no Refs)

89. IN VITRO ACTIVITY OF MISONIDAZOLE AND CYTOTOXIC AGENTS AGAINST HUMAN TUMOR AND BONE MARROW COLONY FORMING UNITS (CFU) UNDER AEROBIC AND HYPOXIC CONDITIONS (MEETING ABSTRACT)

Taetle R, Howell SB, Koessler A
Department of Pathology, University of California at Medical Center, San Diego, CA, 92103
Proc Am Soc Clin Oncol; 1:C-112 1982

The activity of misonidazole (miso) against colonies of human tumor cells grown from xenografts, HL60 promyelocytic leukemia cells, or normal bone marrow granulocyte/macrophage progenitors (CFU-GM) was studied under aerobic and hypoxic conditions. Tumor or bone marrow cells were incubated in 7.5% CO_2 in air with various concentrations of doxorubicin, melphalan, or cisplatin with or without miso (75 or 150ug/ml) for 1 hour, washed and plated. In vitro concentrations of miso approximated plateau and peak serum levels respectively. Miso had no effect on growth of CFU-GM, HL60 colonies, or tumor CFU grown from a human astrocytoma (T24), ovarian carcinoma (T17) or melanoma (T355). Studies were repeated under hypoxic conditions established by gassing incubation tubes with nitrogen bubbled through pyrogallol to remove contaminating oxygen. The average partial pressure of oxgen for hypoxic studies was 34. Under hypoxic conditions, normal CFU-GM, T24 and HL60 cells failed to form colonies. Miso alone further reduced tumor CFU growth under hypoxic conditions. Hypoxic T17 and T355 cells were not less sensitive to chemotherapeutic agents, and miso failed to enhance toxicity of drugs for hypoxic tumor cells. We conclude that under these conditions, miso was not toxic to oxygenated normal, leukemia, or solid tumor CFUs. Miso alone significantly inhibited hypoxic solid tumor CFUs, but did not enhance in vitro toxicity of chemotherapeutic agents for these human cells. (no Refs)

90. AUGMENTATION OF NATURAL KILLER CELL ACTIVITY IN NORMAL AND TUMOR BEARING BALB/C MICE BY LEVAMISOLE (MEETING ABSTRACT)

Laing CA, Japal KM
Howard University Cancer Center, Washington, DC, 20060
Proc Am Assoc Cancer Res; 23:1060 1982

Natural killer cell (NK) activity is an important factor in the immune constituent of young mice and seems to play a role in immune surveillance mechanisms against tumors. Levamisole (LMS) had exhibited immunoregulatory and anti-tumor properties but its effects on NK activity has not been investigated. Whether LMS exert any regulatory function on NK activity in 8 wk old male BALB/c mice was the question posed in this study. Two groups of mice were inoculated with 1x10(6) viable cells (in minimal essential medium) of the 50th transplant generation of a MTV induced mammary tumor which originated from a spontaneous tumor in multiparous BALB/cfC3H female. At the time of inoculation of tumor cells and at 24, 48, and 72 hr thereafter, one group was inoculated with LMS (50 mg/kg of body weight). A third group received LMS alone; controls received no treatment. Administration of LMS caused a significant increase in NK activity of normal non tumor bearing mice above controls. In mice inoculated with tumor cells alone, an increase in NK activity was observed above controls. This could be further augmented above controls by LMS administration in tumor bearing mice. LMS augmentation of NK activity was detected as early as 48 hr and up to 144 hr post inoculation. (no Refs)

91. INCREASED SURVIVAL OF TUMOR-BEARING MICE AFTER ADMINISTRATION OF THYMOSIN PREINCUBATED SYNGENEIC BONE MARROW CELLS (MEETING ABSTRACT)

Cupissol D, Goldstein AL, Serrou B
Centre Paul Lamarque, Montpellier Cedex 34 033, France
Proc Am Assoc Cancer Res; 23:1017 1982

The present results are based on a system directly applicable to man, consisting of bone marrow transplants in C57Bl/6 mice with either methylcholanthrene induced tumor or Lewis tumor. Animals were treated by injection of syngeneic bone marrow cells from non-tumor-bearing mice. If these cells are preincubated in thymosin fraction 5 or alpha 1 before injection there is a significant retardation of tumor growth and metastatic disease followed by significantly increased survival time. In addition, we found that this action: 1) was T lymphocyte dependent and did not occur if bone marrow preincubated with thymosin was treated with anti-thy 1-2 serum; 2) was independent of NK activity. Mice treated with radioactive strontium showed no change for thymosin anti-tumor effects. Tumor bearing mice treated with CDDP (Cis-Platinum) or tumor local radiotherapy (16 grays) associated to thymosin preincubated bone marrow cells also demonstrated a significantly increased survival time as compared to mice treated by chemotherapy or radiotherapy alone. These results are sufficiently encouraging to warrant a randomized trial in order to evaluate the efficacy of administration of autologous bone marrow cells pretreated with thymosin after aggressive chemotherapy in the advanced solid tumor patient. (no Refs)

92. THE PRODUCTION OF ALLOGENEIC CELL-MEDIATED CYTOTOXIC ACTIVITY IN CULTURE CAN BE MODULATED BY ADDITION OF LOW CONCENTRATIONS OF THYMIDINE (MEETING ABSTRACT)

Ehrke MJ, Strzadala L, Mihich E
Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:1001 1982

The possibility that relatively low concentrations of thymidine would affect the development of cell-mediated cytotoxic activity (CMC) in culture was suggested by the observation that 24 hr supernatants from cultures of resident PEC modulate T-cell responses. PEC have been shown to produce and secrete thymidine in relatively high amounts. Three culture conditions were studied: suboptimal S, R:S equals 250:1; optimal S, R:S equals 25:1; supraoptimal S, R:S equal 7.5:1. Thymidine concentrations 10-4M or higher were toxic for the cells in terms of both cell recovery and CMC at all R:S ratios. Concentrations 10-5M and below had little or no effect on the level of CMC developed with R:S ratios of 250:1 or 25:1. Thymidine augmented the CMC in a concentration dependent manner, however, when added to cultures containing supraoptimal S. In fact, 10(-9) thymidine caused up to a 4 fold increase in the CMC. Preliminary data suggest that low concentrations of thymidine may inhibit development of T-suppressor cells in culture and its effect on the CMC may be through selective regulation of this T-cell subset. Thus the amount of thymidine added to cultures in such natural products as fetal calf sserum and that endogenously produced in cultures by macrophage or other cells may have a profound effect on the CMC activity ultimately measured. (no Refs)

93. EFFECTS OF ADRIAMYCIN ANALOGS ON THE DEVELOPMENT OF A CELL MEDIATED CYTOTOXICITY (CMC) RESPONSE GENERATED IN VITRO: COMPARISON WITH ADRIAMYCIN (MEETING ABSTRACT)

Mace K, Schlafli E, Ehrke MJ, Mihich E
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Proc Am Assoc Cancer Res; 23:1000 1982

Antitumor activity of Adriamycin (ADM) in mouse model systems has been shown to involve antitumor host defenses. ADM exerts selective effects on a variety of immune response models, one of which is augmentation of the T-cell mediated cytotoxicity generated in a primary mixed lymphocyte tumor cell culture (MLTC). This system was used to compare the parent compound with four new analogs which have been reported to have high antitumor potency and lower cardiotoxicity than ADM. These are 4'-epiadriamycin; 4'-deoxyadriamycin; 4'-O-methyladriamycin; and 4-demethoxyadriamycin. Spleen responder cells of C57Bl/6 mice were cultured for 4 days with supraoptimal numbers of irradiated (4000 rad) allogeneic P815 mastocytoma cells, resulting in a low control CMC response. The compounds were added at the beginning of the MLTC over a broad concentration range. A drug at a given concentration was considered to be toxic if viable cell recovery and CMC response were below controls. The highest nontoxic concentration of the analogs were as follows: 4-demethoxyADM 10(-8), 4'-O-methylADM 5x10-8M, 4'-deoxyADM 7.5x10-8M, 4'-epiADM 10-7M, ADM 10-7M. In augmenting the CMC response 4'-deoxyADM and 4'-epiADM were as effective as ADM. Maximum augmentation of the CMC was caused by 2.5x10-8M 4'-deoxyADM and 10-7M 4'-epiADM. Preliminary results suggest that 4'-O-methylADM is less effective than the others. 4-DemethoxyADM, over the range of 10(-8) to 10(-9), had no effect on the development of the CMC response. (no Refs)

94. EFFECTS OF CYCLOPHOSPHAMIDE ON IN VITRO MITOGEN STIMULATION AND NK CELL ACTIVITY (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:998 1982

Cyclophosphamide (CY) an anticancer drug was tested for its ability to modulate human lymphocyte response to mitogens and natural killer (NK) cell activity. The inhibition of, or increase in 3H-thymidine incorporation in mitogen stimulate lymphocytes, effect on lymphocyte viability and augmentation of NK cell mediated cytotoxicity (NK-CMC) in 51Cr release assay were the measure of activity of CY in vitro. The results demonstrate that CY had a profound effect on mitogen stimulation of lymphocytes. In almost all cases, CY modulated the stimulation of lymphocytes by phytohemagglutinin (PHA), Concanavalin A (ConA), and Pokeweed mitogen (PWM) by augmenting or suppressing the responses. At low concentration (10 ug/ml) it augmented 46-281% mitogen stimulation. At higher concentration (160 ug/ml) CY had a suppression of 99%. The treatment of lymphocytes with CY at a concentration of 10 ug/ml for 4 to 17 hours augmented the NK-CMC against K-562 target cells. Cyclophosphamide had inhibitory activity on T cells, suggesting that immunomodulation is, perhaps caused by CY action on the regulatory T cells. The results of this study demonstrate that CY is active in vitro and can modulate lymphocyte response to mitogens and NK cell activity against K-562 perhaps by affecting the immunoregulatory cells. (no Refs)

95. EFFECT OF THYMOSTIMULIN ON ACTIVITY OF CERTAIN ENZYMES OF ADENOSINE AND AMP METABOLISM IN RAT LYMPHOCYTES DURING MAMMARY GLAND CARCINOGENESIS.

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Ukr Biokhim Zh; 54(2):154-158 1982

The effect of thymostimulin (TS) on metabolism of adenosine and AMP was studied in random-bred female rats with dimethylbenz(a)anthracene induced mammary gland tumors. Animals received nine injections of TS with 10-day interval between the injections; total dose of TS was 9 mg/rat. In thymus lymphocytes of intact rats, TS produced a 1.3x increase of adenosine deaminase (ADA) activity, 1.6x decrease of 5'-nucleotidase activity, and 1.4x decrease of AMP-aminohydrolase (AH) activity. In spleen lymphocytes, TS administration resulted in a 1.5x decrease of adenylate kinase (AK) activity. The latent period of mammary gland carcinogenesis was characterized by the decrease of ADA, AK, and 5'-nucleotidase activities on day 10 followed by an increase of the activities of the enzymes tested on day 30. TS administration during the latent period of mammary gland carcinogenesis resulted in the decrease of all enzymes tested. These findings indicate that administration of thymosin-like substances can stimulate the functional activity of immunocompetent cells in animals with precancerous conditions. (17 Refs) (In RUS)

96. IN VITRO GENERATION OF HELPER T CELLS AND SUPPRESSOR T CELLS THAT REGULATE THE CYTOLYTIC T LYMPHOCYTE RESPONSE TO TRINITROPHENYL-MODIFIED SYNGENEIC CELLS.

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Transplantation; 33(4):422-426 1982

Helper T cells and suppressor T cells have been generated in vitro that regulate the cytolytic T lymphocyte (CTL) response to trinitrophenyl (TNP)-modified syngeneic cells. B6D2F1 helper cells generated to TNP-modified parental (P1) cells augment the CTL response to those P1-TNP-modified antigens but not to P2-TNP-modified antigens. The generation of these helper T cells requires the presence of splenic adherent cells and these helper T cells are radioresistant. A soluble factor can be obtained from the helper T cell cultures that can also augment the CTL response. The suppressor T cells generated in culture do not demonstrate the specificity observed with the helper T cells; however, they are antigen-dependent in their induction. Whether helper or suppressor activity is obtained depends upon the length of time cells are cultured in vitro. (Author abstract) (26 Refs)

97. ANTAGONISM OF CONCANAVALIN A CAPPING IN PHORBOL ESTER-ACTIVATED LYMPHOCYTES BY CALMODULIN INHIBITORS AND CERTAIN AMINO ACID ESTERS.

Kwong CH, Mueller GC
(c/o Mueller) McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 42(6):2115-2120 1982

The compound 12-O-tetradecanoylphorbol-13-acetate (TPA), an effective tumor promoter in mouse skin and comitogen in bovine lymphocytes, rapidly stimulates concanavalin A-mediated cap formation in the latter cells. The ability of different phorbol derivatives to facilitate the capping reaction correlates well with their potencies as lymphocyte comitogens and as tumor-promoting agents. This effect of TPA on capping in bovine lymphocytes, which is apparent within min, is neither mimicked nor altered by dibutyryl cyclic adenosine 3':5'-monophosphate or cyclic guanosine 3':5'-monophosphate. Cytochalasin D, a microfilament-disrupting agent, inhibits cap formation, thereby suggesting the participation of microfilaments in the response. benzoyl tyrosine ethyl ester selectively inhibits the TPA-stimulated cap formation, whereas benzoyl tyrosinamide is inactive. A comparison of related amino acid derivatives reveals that their activities are dependent on the nature of both the amino acid side chain and the carboxyl end blocking group. Trifluoperazine and N-(6-aminohexyl)-5-chloronaphthalenesulfonamide, known inhibitors of the calmodulin-dependent processes, also selectively block the TPA-stimulated cap formation, whereas trifluoperazine sulfoxide, a less effective calmodulin antagonist, is relatively inactive. These data suggest that the stimulation of capping by TPA involves the activation of a calmodulin-dependent process which may also be regulated by the function of an esterase. (Author abstract) (32 Refs)

98. 12-O-TETRADECANOYLPHORBOL-13-ACETATE ACTIVATES A LOW LYT2 ANTIGEN EXPRESSING, POORLY CYTOLYTIC ALLOIMMUNE T KILLER SUBPOPULATION (MEETING ABSTRACT)

Munger WE, Lindquist RR
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Fed Proc; 41(3):415 1982

We examined the effect of tumor promoting phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) on murine alloimmune cell mediated cytotoxicity (CMC) using a 3 hour 51-Chromium (51-Cr) release assay. Previously we showed that TPA but not the inactive analogue 4 alpha phorbol-12,13-didecanoate (4alphaPDD) augments the killing ability of alloimmune splenocytes. The augmented killers remain H-2 specific, express Thy 1.2 antigen, and augmentation is not dependent upon macrophages. Normal, nonimmunized splenocytes do not contain these killers. More recently, using monoclonal anti-Lyt 1.2 and anti-Lyt 2.2 antibodies and rabbit complement (RC), we find that a poorly cytolytic Lytl-negative, low Lyt 2 expressing splenocyte subpopulation accounts for most of the augmented killing. For example, pretreatment of H-2b anti-H-2d splenocytes with a 1:2000 dilution of anti-Lyt 2.2 antibody (Ab) plus RC eliminated killing against H-2d targets in the presence or absence of TPA. However, with a 1:3000 dilution of anti-Lyt 2.2 Ab plus RC non-TPA-treated splenocytes killed 11.7 + 1.2% whereas with 1 ng/ml TPA Treatment killing rose to 29.6 +/-2.0%. Anti-Lyt 1.2 Ab and RC reduced control killing 50% but did not effect TPA augmentation. RC alone affected neither TPA-treated nor non-TPA-treated killers. In summary, TPA augments specific alloimmune CMC primarily by increasing the killing ability of CTL which express low levels of Lyt 2 antigen. (no Refs)

99. THE ROLE OF IMMUNOSUPPRESSANTS IN LYMPHOCYTE FUNCTION.

Winkelstein A
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The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

Effects of cytotoxic drugs on lymphocyte numbers, functional activities, and immunosuppressive properties are discussed. Such effects are closely correlated with the drugs' cell cycle specificities. Specific agents discussed include azathioprine, cyclophosphamide, methotrexate, and chlorambucil. Humoral and cell-mediated responses, toxicities, and use of corticosteroids are considered. (128 Refs)

100. DIFFERENTIAL EFFECTS OF TUMOR PROMOTERS ON IMMUNE CELL SUBPOPULATIONS (MEETING ABSTRACT)

Devens BH, Hannon MA
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Fed Proc; 41(3):331 1982

The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) has numerous biological activities. Previous studies have indicated that TPA may inhibit the immune response system. The present work demonstrates that TPA blocks the ability to antigenically stimulate cell mediated cytotoxicity (CMC) in vitro, but has no effect on the expression of cytotoxicity by immunized cytotoxic T cells. Splenocytes from nonimmunized C57Bl/6 mice were treated with TPA for 1 hour, washed extensively, and co-cultured for 6 days with the sensitizing tumors P815 (allogeneic) or EL-4 (syngeneic). At the end of the culture the degree of immune response generated was assessed by a ^{51}Cr release assay. TPA blocked the generation of cytotoxicity in a dose dependent fashion. TPA at .01 ugm/ml consistently blocked all responses and .001 ugm/ml partially blocked the generation of CMC. TPA treated splenocytes remained viable following treatment. Only those structural analogues of TPA which could promote tumors were able to block the generation of CMC. In marked contrast to the ability of promoters to block the generation of CMC, promoters were totally ineffective in blocking the expression of cytotoxicity by immunized spleen cells. This was true both for responses generated by in vivo immunization and in vitro sensitization. (no Refs)

101. ALTERATION OF THE IMMUNE REACTIONS BY WHOLE-BODY AND LOCAL MICROWAVE HYPERTHERMIA IN NORMAL AND TUMOUR-BEARING ANIMALS. REVIEW OF OWN 1976-1980 EXPERIMENTS.

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Br J Cancer; 45(Suppl5):122-126 1982

Alteration of both non-specific and specific immune functions in normal and tumor-bearing animals exposed to thermal doses of microwave radiation (microwave hyperthermia: MwH) are reviewed. In general, whole-body MwH led to inhibition of various immune reactions, while local heating of tumor stimulated the function of macrophages and/or lymphocytes in tumor-bearing hosts. Usually, daily sessions of 2,450 or 3,000 megaHertz whole-body microwave radiation elevated rectal temperature by 3-4 C and inhibited growth of sarcomas 180 and L1. Later studies showed that although whole-body MwH led to temporary regression of sarcoma L1, the number of lung metastases was increased. Mice irradiated prior to tumor transplantation showed increased tumor growth and an increased incidence of spontaneous lung metastases. Diminished resistance to the formation of lung nodules could be adoptively transferred by bone marrow cells, but not by spleen or thymus cells, obtained from MwH-treated donors. MwH also inhibited in vivo phagocytosis and reactivity of immunocompetent T-lymphocytes. Irradiation of neoplastic tissue in tumor-bearing rats inhibited tumor growth and stimulated cell-mediated immunity. (14 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

102. IN VITRO GENERATION OF TUMORICIDAL PROPERTIES IN HUMAN ALVEOLAR MACROPHAGES FOLLOWING INTERACTION WITH ENDOTOXIN.

Sone S, Moriguchi S, Shimizu E, Ogushi F, Tsubura E
Third Dept. Internal Medicine, Univ. Tokushima, Sch. Medicine, Tokushima 770, Japan
Cancer Res; 42(6):2227-2231 1982

Human alveolar macrophages (AM) obtained by bronchoalveolar lavage from healthy nonsmoking donors exhibited primarily low levels of cytolytic activity against allogeneic tumor target cells. These AM acquired enhanced capacity to kill tumor cells following a 24-hr incubation in vitro with endotoxin [lipopolysaccharide (LPS)]. Maximal tumoricidal activity of LPS-activated AM as measured by lysis of tumor target cells was obtained after incubation with tumor cells for 72 hr. LPS-activated AM lysed allogeneic tumor cell lines of different origins but did not affect normal, nonneoplastic cells. We conclude the LPS induces human AM to become tumoricidal. This method should be useful in studies on therapeutic agents enhancing AM-mediated cytotoxicity in situ. (Author abstract) (38 Refs)

103. SUPEROXIDE RELEASE BY PULMONARY ALVEOLAR MACROPHAGES FOLLOWING ACTIVATION TO A TUMORICIDAL STATE (MEETING ABSTRACT)

Drath DB, Kahan BD
University of Texas Medical School, Houston, TX, 77030
Fed Proc; 41(3):846 1982

Pulmonary alveolar macrophages (PAM) upon activation, are involved in tumor cell destruction. To date, however, the mechanism(s) of tumoricidal activity remain largely unexplained. We have therefore examined the action of muramyl dipeptide (MDP) and lipopolysaccharide (LPS), agents known to activate macrophages to a tumoricidal state in vitro, for their ability to enhance release of reactive oxygen metabolites from murine PAM. Our results indicate that LPS (0.1ug/ml) but not MDP (10ug/ml) when incubated with PAM overnight causes a 3-fold elevation in superoxide release from nonstimulated or resting PAM. Muramyl dipeptide and LPS cause increases in superoxide release from zymosan-stimulated PAM of approximately 30% and 50% respectively when compared to control PAM. Incorporation of either agent in multilamellar liposome vesicles composed of phosphatidylserine and phosphatidylcholine (3:7 mole ratio) enabled smaller concentrations of the activating agents to enhance superoxide release from zymosan-stimulated PAM following shorter periods of incubation. Empty liposomes had no effect on superoxide generation and liposome-encapsulated agents did not have significantly different effects on resting PAM than the free agents. We conclude that agents known to activate macrophages to a tumoricidal state elevate superoxide release suggesting a possible involvement of this oxygen metabolite in tumor cell destruction. (no Refs)

104. ANALYSIS OF PROTECTIVE MECHANISMS: RELATIONSHIP BETWEEN ACTIVITY OF NON-IMMUNE MACROPHAGES AND IMMUNE RESPONSES.

Yoshikai Y
Departement of Microbiology, Cancer Res. Inst., Faculty Medicine, Kyushu Univ., Fukuoka 812, Japan
Fukuoka Igaku Zasshi; 72(12):647-666 1981

The effect on immune response due to changes in the activity of non-specific macrophages was examined. Macrophage (M phi) stimulation was achieved by injecting Corynebacterium parvum or diethylstilbestrol (DES); and M phi blockade was induced by applying carbon particles or carrageenan Type II. Up to the third day after infection, the growth of bacteria, Listeria monocytogenes, was seen to increase in the M phi blockade group compared to the non-treated control group, whereas a marked suppression was seen in the M phi stimulated group. On the eighth day, however, no difference was seen among the three groups on the number of bacteria. The delayed type footpad reaction (DFR) was induced in the M phi blockade group with a lower antigen dose compared to the non-treated group. A much higher dose was needed to induce the DFR in the M phi stimulated group. The acquired resistance of cell mediated immunity (CMI) against reinfection was higher in the M phi blockade group than that in the non-treated group; CMI was lowest in the M phi stimulated group. When immunized with sheep red blood cells obtained: the DFR was shown with the least antigen dose in the M phi blockade group; the M phi stimulated group needed the highest dose to induce the reaction. Cyclophosphamide showed an additive effect to M phi blocking reaction. Sensitized suppressor T cells were produced with a lower dose of antigen in the M phi blockade group compared to that used in the other two groups. The intake of 51Cr-SRBC by the liver was significantly decreased in the M phi blockade group; no significant difference was observed between the non-treated group and the M phi stimulated group. No significant difference among the three groups was seen in the intake of 51Cr-SRBC by the spleen, however. There appeared to be of little effect on the lymphocytic function by the treatment of DES or carbon particles. These results suggest that when the activity of non-immune macrophages is high, the amount of effective antigen decreases, and consequently the immune response is weak; conversely, when the activity of non-immune macrophages is low, few antigen is excluded, and is therefore available for inducing strong immune response. (111 Refs) (In JPN)

105. CYTOTOXICITY ON TUMOR CELLS OF HUMAN MACROPHAGES: FUNCTIONAL STATUS OF TUMOR-ASSOCIATED EFFECTOR CELLS.

Mantovani A, Bordignon C, Biondi A, Introna M, Allavena P, Tedesco, Ruco L
Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea, 62, 20157 Milan, Italy
Adv Exp Med Biol; 141:99-108 1982

Tumoricidal activity of human mononuclear phagocytes is reviewed. The nonspecific cytotoxicity of macrophages isolated from ascitic and solid ovarian tumors was measured using TU5 tumor cells as targets. Blood monocytes from ovarian cancer patients had cytolytic activity somewhat lower (p less than 0.01) than control effectors, although there was wide overlap between the two groups when the capacity of monocytes to mature into macrophages was taken into account. Various stimuli such as interferon (IF), lymphokines and endotoxin augmented the cytotoxicity of tumor-associated macrophages (TAM). In a few patients macrophages from the ascitic and solid neoplasm showed similar activation of TAM, whereas TAM from two additional solid tumors were less responsive than effectors from ascites. In an effort to further investigate the tumor-host relationship at the tumor site, the susceptibility of primary ovarian carcinoma cultures to macrophage cytotoxicity was investigated. Ovarian tumor cells from different donors were heterogeneous in their interaction with mononuclear phagocytes. Some tumor cells were resistant to lysis by unstimulated effectors. Growth of these macrophage-resistant tumor cells was usually stimulated by macrophages. A similar heterogeneity of susceptibility was observed when IF or lymphokine stimulated effectors were used. (37 Refs)

106. MECHANISMS OF TARGET RECOGNITION AND DESTRUCTION IN MACROPHAGE-MEDIATED TUMOR CYTOTOXICITY.

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Fed Proc; 41(6):2212-2221 1982

Macrophages can be activated to kill neoplastic cells selectively and efficiently. Recent studies from this laboratory on mechanisms of target recognition and injury operative in such lysis have centered on the binding of tumor targets to and the secretion of a cytolytic protease (cytolytic factor [CF]) by activated murine macrophages. Activated macrophages selectively and extensively bind neoplastic cells; nonselective binding of a low degree is seen between numerous other cell pairs. The selective binding of three nonadherent tumors, which is much firmer than the nonselective binding, appears to depend on shared recognition structures contained within plasma membranes of the three tumors. Activated macrophages also secrete a potent, cytolytic, serine protease of mol wt approx 40,000. Secretion of CF is closely correlated with activation for cytolysis, and specific protease inhibitors of CF block macrophage-mediated cytotoxicity. Binding of tumor cells to activated macrophages triggers augmented secretion of CF. Several lines of evidence indicate that the capacity for selective binding and the capacity for secreting CF are separate and independently regulated functions of activated macrophages and that each is necessary but not sufficient for completion of macrophage-mediated tumor cytotoxicity. Analysis of the complete lytic interaction between activated macrophages and tumor cells suggests that binding and then secretion of CF are sequentially involved. These data have been integrated into a minimal hypothetical model, which suggests that macrophage-mediated tumor cytotoxicity is a multistep event encompassing (1) selective binding of tumor cells to the surface of activated macrophages and (2) secretion of multiple lytic effector substances, including CF, from the activated macrophages. (Author abstract) (35 Refs)

107. MACROPHAGE ACTIVATION FOR TUMOR CYTOTOXICITY: REACTIVITY OF PERITONEAL AND BONE MARROW MACROPHAGES.

Ruco LP, Meltzer MS, Leonard EJ, Tomisawa S, Gallily R, De Chatelet LR, Patriarca P, Clark RA, Rossi F
Second Inst. Pathological Anatomy, Univ. Rome, Viale Regina Elena 324, 00161 Rome, Italy
Adv Exp Med Biol; 141:85-97 1982

Various studies concerning tumor cytotoxicity induced by murine (CIMLAM) lymphokine-activated macrophages are reported. The following aspects of CIMLAM are included course of lymphokine activation (LA), effect of time in culture prior to LA, lymphokine responsiveness of resident and inflammatory macrophages, and effect of x-irradiation. Peritoneal macrophage function was also studied during acute inflammation. Reactive cells differentiated to a non-reactive stage within 24 hr and either in vivo BCG activated or in vitro lymphokine activated macrophages maintain their status for a few hr. The short-lived nature of both macrophage tumoricidal capacity and the capacity of precursor cells to be activated by lymphokines may function as negative feedback mechanisms in immune reactions. The close association found between the frequency of macrophages with intracytoplasmic peroxidase-positive granules and lymphokine reactivity of the cell population may indicate that lysosomal peroxidase may be involved in lymphokine activation for tumor cytotoxicity. (11 Refs)

108. HOST MACROPHAGES ARE INVOLVED IN SYSTEMIC ADOPTIVE IMMUNITY AGAINST TUMORS.

Van Loveren H, Snoek M, Den Otter W
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Experientia; 38(4):488-490 1982

The positive systemic therapeutic results obtained with adoptive transfer of immune spleen cells could not be reproduced in macrophage depleted mice. Thus, host macrophages are involved in systemic adoptive immunity against tumors. (Author abstract) (15 Refs)

109. REGULATION OF GRANULOCYTE AND MACROPHAGE COLONY-STIMULATING FACTOR PRODUCTION BY PHYTOHAEMAGGLUTININ-TREATED BLOOD MONONUCLEAR CELLS.

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Leuk Res; 6(1):71-79 1982

Medium conditioned by incubation of phytohemagglutinin (PHA: 25 ul/ml)-stimulated human peripheral blood mononuclear cells for 7 days was tested for colony-stimulating activity (CSA) for granulocyte-macrophage colony-forming cells from normal bone marrow. The conditioned medium gave two peaks of stimulation: one at a concentration of 5-10% (peak I) and the other at a concentration of 20% (peak II). Stimulation at 15% was considerably less. With stimulation by peak I material most of the colonies were neutrophilic on days 7 and 14. With peak II material few colonies were seen at 7 days, but at 14 days colonies contained macrophages or mixtures of macrophages and neutrophils. Removal of adherent cells prior to culture abrogated all stimulating activity of both peaks. However, supernatant of conditioned medium incubated with adherent cells for 1 wk ('reconditioned' medium) stimulated colony growth. PHA-stimulated mononuclear cells appear to act on adherent cells releasing colony-stimulating factor. (20 Refs)

110. CHARACTERIZATION OF THE RECOGNITION OF TARGET CELLS SENSITIVE TO OR RESISTANT TO CYTOLYSIS BY ACTIVATED MACROPHAGES. II. COMPETITIVE INHIBITION OF MACROPHAGE-DEPENDENT TUMOR CELL KILLING BY MITOGEN-INDUCED, NONMALIGNANT LYMPHOBLASTS.

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Cell Immunol; 68(1):155-164 1982

We have previously reported that tumoricidal rat macrophages can distinguish quiescent normal lymphocytes from concanavalin A (Con A)-stimulated lymphocytes and thymic lymphoma cells on the basis of their ability to compete for the macrophage-dependent cytolysis of a sensitive tumor cell line. The present study was undertaken to determine (a) whether recognition was related to the proliferative response induced by Con A stimulation and (b) whether the competition of cytolysis was dependent upon the binding of sensitive target cells to activated macrophages. These possibilities were tested by examining Con A-treated lymphocytes in different functional stages of the Con A response with respect to their ability to compete either for cytolysis or binding of of a tumor cell line susceptible to both activities. The results show that the ability to complete for either function was acquired coincidentally with the Con A-induced proliferative response. This competitive activity was not due solely to the presence of Con A in the culture medium nor to culture of unstimulated lymphocytes but rather required a blastogenic response to the mitogen. Blast-transformed nonproliferative cells (96 hr post-Con A stimulation) were as competitive as cells which had been stimulated to reinitiate DNA replication by treatment with Interleukin 2. Thus, competition for cytolysis is a consequence of blastogenesis rather than proliferation per se and operates mechanistically by competing for the binding of target cells to activated macrophages, an event known to be a necessary prerequisite to cytolysis. (Author abstract) (19 Refs)

111. ROUS SARCOMA VIRUS-INDUCED TUMORS IN MICE - I. MACROPHAGE-MEDIATED NATURAL CYTOTOXICITY.

Giovarelli M, Landolfo S, Whitmore AC, Forni G
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Eur J Cancer Clin Oncol; 18(3):307-315 1982

Lymphoid cells from normal untreated A.SW mice showed a cell-mediated cytotoxicity (CMC) towards Rous sarcoma virus-induced tumor lines in a 48-hr microcytotoxicity assay in vitro, using 3[H]-thymidine prelabeled tumor cells. The tissue distribution of this natural CMC shows high levels of activity in th peritoneal cavity, intermediate levels in bone marrow and spleen, and low levels in lymph node, peripheral blood and thymus. Natural CMC of unstimulated resident peritoneal cells against tumor cells was also found in several strains of mice. This was not dependent on the donor's age, since similar levels appeared in mice aged 1-40 wk. Passage through nylon wool columns or adherence to the plastic surface of resident peritoneal cells removed cytotoxic activity. By contrast, adherent cells displayed significant CMC levels. Treatment with carbonyl iron powder and magnet decreased peritoneal cell cytotoxicity when performed once and abolished it when repeated. All these results suggest that in mice, natural cytotoxicity against Rous sarcoma virus-induced tumors is primarily mediated by macrophages or macrophage-like cells. (Author abstract) (30 Refs)

112. THE BIOLOGICAL EFFECTS OF CARRAGEENAN AND OTHER SULFATED POLYSACCHARIDES WITH PARTICULAR ATTENTION TO IMMUNOLOGICAL AND CARCINOGENIC PROPERTIES.

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Ugeskr Laeger; 144(12):860-863 1982

A review of studies on the biological effects of carrageenan shows that induction of colorectal cancer was observed in rats following long-term oral administration of degraded carrageenan. Native (high-molecular-weight) is not known to possess carcinogenic properties. Carrageenan stimulates tumor growth secondarily. The cocarcinogenic effect of carrageenan may be due to its immunosuppressive properties (toxic effect on macrophages and activation of macrophage suppressor cells). (29 Refs) (In DAN)

113. AUGMENTATION OF METASTASIS FORMATION BY THIOGLYCOLLATE-ELICITED MACROPHAGES.

Gorelik E, Wiltrout RH, Brunda MJ, Holden HT, Herberman RB
Surgery Branch, NCI, Bethesda, MD, 20205
Int J Cancer; 29(5):575-581 1982

Inoculation of thioglycollate-elicited peritoneal exudate cells (PEC) into C57BL/6 mice reduced the rate of lung clearance of several intravenously (iv) injected murine tumor cells, and increased by up to 100-fold the number of artificially-induced metastatic lung nodules produced by the iv injection of B16 melanoma or Lewis lung carcinoma (3LL) tumor cells. Maximum effects were observed when PEC were injected either before, or shortly after, tumor cells. Modulation of lung clearance or metastasis formation was observed only with PEC and not with a variety of other cells, such as splenocytes, thymocytes, P815 mastocytoma cells, or several macrophage-like cell lines (PU5-1.8 and IC-21). Lysates of PEC were as efficient in reducing lung clearance and augmenting metastasis formation as were intact viable PEC. Lysates of other cell types, including P815 and the macrophage-like cell lines, were unable to produce these effects. PEC populations, enriched for macrophages by adherence to plastic or by percoll density gradient sedimentation, also increased the number of B16-induced artificial metastasis, implicating the macrophage as the cell responsible for these observations. (Author abstract) (25 Refs)

114. THE ROLE OF MACROPHAGES IN CONTROLLING POST-OPERATIVE METASTASIS OF 3LL (MEETING ABSTRACT)

Brodt P, Segal S
Department of Anatomy, McGill University, Montreal, Quebec H3A 2B2, Canada
Proc Am Assoc Cancer Res; 23:1037 1982

It was previously reported that the metastatic spread of the Lewis lung carcinoma (3LL) is low during the growth of a local tumor in the footpad, but greatly enhanced after its removal by amputation of the leg. The aim of the present study was to investigate the role of macrophages in the control of metastasis prior to and following surgery. Mice injected in the footpad with a lethal dose of tumor 3LL received various doses of either carrageenan -- a polysaccharide toxic to macrophages or tuftsin -- a peptide known to stimulate macrophage activity in vivo. The agents were administered ip prior to, simultaneously with, or following the removal of the local tumor. The following observations were made: 1) When injected ip but not into the tumor, carrageenan was effective in enhancing metastasis at every concentration and regimen applied, but more limited in mice whose local tumor was not removed. 2) Mice injected with carrageenan 7 days prior to tumor removal showed the most extensive increase in metastasis, as compared to mice injected simultaneously with or following amputation. 3) The administration of tuftsin was successful in reducing post-amputation metastasis only when injected both prior to and following amputation. These results support the existing body of evidence for the host-protective role macrophages play against metastasis and suggest that in the current tumor model this role is more significant during the growth of the primary tumor. They also indicate the existence of other mechanisms in the control of metastasis during tumor growth. (no Refs)

115. REGULATION OF MACROPHAGE TUMORICIDAL ACTIVITY BY CELLULAR CHOLESTEROL AND FATTY ACID (MEETING ABSTRACT)

Schlager SI, Madden L
Department of Microbiology, University of Notre Dame, Notre Dame, IN, 46556
Fed Proc; 41(3):846 1982

Activation of mouse peritoneal macrophages (M) by lymphokine (LK) has been shown to be correlated with unique changes in M lipid composition; M content of cholesterol (CHOL) and unsaturated fatty acid (UFA) increased as the cell became tumoricidal and returned to control levels as tumoricidal activity was lost. The role of CHOL and UFA in M in regulating their cytotoxic activity was studied. Casein-induced peritoneal M were cultured in tissue culture medium containing 10% delipidized serum; the cells were enriched in CHOL or linolenic acid (18:3) by supplementing the medium with 500 ug/ml of the appropriate lipid. At various times after culture, lipid composition of the M was determined; replicate M were tested for their ability to kill 1023 tumor cells. Within 1 hr of culture, M showed a 3 to 4-fold increase in CHOL or 18:3 content. The 18:3 enriched cells were markedly tumoricidal whereas controls cultured in delipidized medium alone or enriched with saturated FA were not cytotoxic. CHOL-enriched M were not tumoricidal; indeed, these cells were inhibited in their killing after treatment with LK compared to M cultured in delipidized medium with LK alone. These results suggest that UFA aid, whereas CHOL negates, expression of M tumor cytotoxicity. (1 Ref)

116. GENETIC ASPECTS OF MACROPHAGE ACTIVATION FOR TUMOR CYTOTOXICITY.

Boraschi D, Tedesco
Istituto di Ricerche Farmacologiche 'Mario Negri', Milano, Italy
Adv Exp Med Biol; 141:119-128 1982

Defective macrophage activation was studied in mouse strains A/J and P/J with low macrophage tumoricidal activity in comparison with strain C3H/HeN with high and C3H/HeJ with low activity. Cells from these strains were compared for their ability to respond to chemotactic stimuli, to phagocytize IgG-opsonized RBC, and to express the cytochemical marker peroxidase. Inflammatory events took place normally in A/J mice comparable to those in the control strains. P/J macrophages showed a profound abnormality in phagocytic capacity. P/J lymphocytes also showed a profound defect in macrophage activating lymphokine (MAF) activity. When P/J mice were tested for production of two other lymphokines, the chemotactic factor (LDCF) was normal whereas they were defective for production of immune interferon. Macrophages from P/J mice showed a difference in reactive mononuclear phagocytes in response to two activation stimuli. As in the other studies, the defects in the macrophages of C3H/HeJ and A/J mice were phenotypically similar while those of P/J mice were distinct. Macrophages of A/J and P/J were sensitive to lipopolysaccharide (LPS) toxicity in vitro in contrast to C3H/HeJ, indicating a genetic difference. By genetic analysis it was possible to demonstrate C3H/HeJ and A/J macrophage defects had a different genetic basis. Further studies with the use of backcross mice showed that the A/J tumoricidal defect is controlled by at least two genes. The lymphocyte proliferation defects in response to LPS appears to be under the control of a single gene. (22 Refs)

117. MACROPHAGE ORIGIN OF REED-STERNBERG CELLS: AN IMMUNOHISTOCHEMICAL STUDY.

Payne SV, Wright DH, Jones KJ, Judd MA
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J Clin Pathol; 35(2):159-166 1982

In an immunohistochemical study of 26 biopsies from 24 patients with Hodgkin's disease a granular staining pattern for alpha-1-antitrypsin (alpha1AT) and alpha-1-antichymotrypsin (alpha1ACT) was seen in Reed-Sternberg (RS) cells and mononuclear Hodgkin's (H) cells in over half the cases. The pattern of staining for these antiproteases seen in RS and H cells has previously only been observed in normal and malignant cells of the monocyte/macrophage lineage within the lymphoreticular system. A faintly granular evenly distributed staining for IgG was found in viable RS and H cells. This staining was associated with a similar distribution of both light chains but not J chain, suggesting that the immunoglobulin had not been synthesized by these cells but had been taken up from the extracellular environment. It is suggested that this uptake is an active process occurring in viable RS and H cells, possibly via Fcgamma receptors and further supports an origin from cells of the monocyte/macrophage lineage. IgA, IgD, albumin, fibrinogen, C1q, C4 and C3 were present in some cells, IgM was more rarely found and lysozyme was absent. The fact that cells staining for these serum proteins generally showed signs of degeneration and that the extent of staining correlated with the mol wt, but not serum concentration, of the protein suggests that they are passively acquired by dead or dying cells and thus represent a separate phenomenon from IgG uptake. The function of IgG uptake and accumulation by RS cells and the alpha1AT and alpha1ACT markers may prove of use in identifying the macrophage subtype from which these cells are derived. (Author abstract) (39 Refs)

118. SOLUBLE CYTOSTATIC FACTOR(S) RELEASED FROM HUMAN MONOCYTES. I. PRODUCTION AND EFFECT ON NORMAL AND TRANSFORMED HUMAN TARGET CELLS.

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Scand J Immunol; 15(3):311-318 1982

Human monocytes activated with lymphokines after 3-7 days of in vitro maturation released stable cytostatic factor(s) (CF), as determined by reduction of [methyl-3H]thymidine incorporation and cell counts in target cell cultures. Lipopolysaccharide from Escherichia coli slightly enhanced the release of CF. The CF release was greatest at an intermediate stage of the in vitro monocyte maturation to large, macrophage-like cells. Three transformed human cell lines (NHIK 3025, K-562, and U-20S) and normal skin fibroblasts were consistently inhibited by CF. Normal human mesothelial cells were variably affected, while normal human lymphocytes proliferating in response to allogeneic cells in mixed lymphocyte culture were not inhibited. Further analysis of CF may disclose one of the mechanisms whereby human monocytes and macrophages inhibit growth of human tumor cells. (Author abstract) (34 Refs)

119. TUMORICIDAL ACTIVITY OF HUMAN MONOCYTES: ACTIVATION BY LIPOSOME-ENCAPSULATED MURAMYL DIPEPTIDE (MEETING ABSTRACT)

Erickson KL, Schroit AJ, Stevenson HC, Fidler IJ
National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD
Fed Proc; 41(3):845 1982

These studies were designed to determine whether multilamellar lipid vesicles, liposomes, containing muramyl dipeptide (MDP) would render human peripheral blood monocytes tumoricidal. Homogenous preparations of monocytes were obtained by leukapheresis and countercurrent centrifugation elutriation. Tumoricidal activity of monocytes could be generated by their incubation with LPS (lipopolysaccharide) or MDP. The phagocytosis of liposomes containing either hydrophilic or a lipophilic derivative of MDP generated optimal monocyte-mediated cytotoxicity against human melanoma and choriocarcinoma cells. Liposomes composed of phosphatidylcholine and phosphatidylserine at a 7:3 mole ratio were maximally phagocytosed by the monocytes. Two populations of monocytes sorted with the FACS (fluorescence-activated cell sorter) by the presence or absence of phagocytosed liposomes were both tumoridical toward the target cells. This activation was not due to the release of MDP from the liposomes into culture. The ability to activate monocytes by liposome-entrapped MDP is attractive since liposomes injected into the circulation are cleared by phagocytic cells which have been shown to play a role in host defences against invading neoplasms. (no Refs)

120. ACCESSORY FUNCTION OF A SMALL RADIORESISTANT SPLEEN CELL POPULATION IN THE GENERATION OF T-CELL-MEDIATED CYTOTOXICITY.

Dupuy D'Angeac A, Reme T, Pla M, Colombani J
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Cell Immunol; 68(1):1-15 1982

A subpopulation of radioresistant splenocytes (RSCs) was examined for its ability to act as accessory cells in the generation of cytotoxic thymus-dependent lymphocytes (CTLs). RSCs provided accessory functions to nylon wool-filtered spleen T cells or mature thymocytes acting as responders to allogeneic spleen T cells or mature thymocytes. The participation of Ia antigens in the accessory process was investigated using anti-Ia sera directed against the products of I-A and/or I-E/C subregions. We found that RSC accessory function was dependent upon cells expressing I-A or I-E/C antigens. Preincubation of spleen T cells with RSCs increased the ability of these cells to stimulate allogeneic spleen T cells regardless of whether RSCs were allogeneic, or semisyngeneic to the stimulator T cells. (Author abstract) (33 Refs)

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY

121. EFFECTS OF BCG AND CYCLOPHOSPHAMIDE ON THE SPONTANEOUS AND ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY OF PERITONEAL AND SPLEEN LYMPHOCYTES OF ACI/N RATS.

Saijo N, Irimajiri N, Ozaki A, Takizawa T, Beppu Y, Shibuya M, Shimizu E
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Gan; 73(2):270-277 1982

The effects of BCG and cyclophosphamide on the antibody-dependent cell-mediated cytotoxicity (ADCC) and natural killer (NK) activity of spleen and peritoneal lymphocytes were serially examined after treatment. The changes of ADCC and NK activity were different in peritoneal and spleen lymphocytes according to the route and timing of administration. The decrease of NK activity induced by cyclophosphamide is not marked, and the degree of decrease depends on the timing of cyclophosphamide administration. The ADCC and NK activity of peritoneal lymphocytes after intravenous BCG administration were elevated 7 days after treatment, but the NK activity of spleen lymphocytes was decreased. On the other hand, the NK activities of peritoneal and spleen lymphocytes were elevated in rats given intraperitoneal BCG. Spleen lymphocytes and peritoneal lymphocytes from rats given intravenous BCG suppressed tumor growth in the Winn test during the early tumor-bearing stage. The spleen lymphocytes with low NK activity in rats given intravenous BCG strongly suppressed the NK activity of normal spleen lymphocytes. (Author abstract) (30 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

122. HETEROGENEITY OF SOLUBLE T CELL PRODUCTS. I. PRECURSOR FREQUENCY AND CORRELATION ANALYSIS OF CYTOTOXIC AND IMMUNE INTERFERON (IFN-GAMMA)-PRODUCING SPLEEN CELLS IN THE MOUSE.

Krammer PH, Marcucci F, Waller M, Kirchner H
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Eur J Immunol; 12(3):200-204 1982

In this study, the precursor frequency, relationship and activity of murine splenic cytotoxic and immune interferon (IFN-gamma)-producing cells has been determined. C57BL/6 spleen cells were activated by concanavalin A (Con A) and subsequently grown in microcultures under limiting dilution conditions. The progeny of cells plated in microcultures was divided and tested for (a) total cytotoxic activity on EL4 (H-2b) tumor target cells in the presence of Con A to nonspecifically attach the killer to the target cells, and (b) the quantity of IFN-gamma released by Con A stimulation. Cytotoxic T lymphocytes and IFN-gamma producing cells were present in Con A-activated C57BL/6 spleen cells at a high frequency of approx one out of three and one out of two cells, respectively. IFN-gamma could be released from both noncytotoxic and a large fraction of cytotoxic T cells and the cytotoxic activity was not necessarily associated with IFN-gamma release. In a few selected cultures with a progeny of cells plated at a low cell number (up to 10/well) very high IFN-gamma titers (greater than 10,000 U/ml) could be found. These results provide the first frequency estimate of IFN-producing cells and are discussed with respect to the physiological role of IFN-gamma release from T cells. (Author abstract) (18 Refs)

123. HUMAN NATURAL KILLER-LIKE ACTIVITY AGAINST MOUSE SPLEEN CELLS.

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Eur J Immunol; 12(3):222-227 1982

Unstimulated human peripheral lymphocytes were cytotoxic for normal mouse spleen cells and suppressed the in vitro antibody plaque-forming cell (PFC) response of these cells to sheep red blood cells and dinitrophenylated Ficoll. The cells in the lymphocyte population that were responsible for the immunosuppression had properties of natural killer (NK) or NK-like cells in that they were: (a) non-E-rosetting, (b) nonadherent, (c) unaffected by treatment with anti-human immunoglobulin plus complement, (d) cytotoxic against an established human NK target, K562 leukemic cells, and (e) partially inactivated by mitomycin C. Addition of the human NK-like cells to mouse spleen cell cultures at the time of antigen addition and at an effector cell to target cell ratio as low as 0.67:1 resulted in 85 to 96% suppression of the PFC response. Addition of NK-like cells to cultures 18 hr before harvesting in 5-day cultures required higher concentrations and ratios (2.7:1) of effector to target cells to significantly suppress the PFC response. The data suggest that human NK-like activity in suppression of the mouse PFC response is due to killing of the targets. The mouse spleen cell PFC system represents a potential model for assessment of human NK activity that is quite dramatic in its effect and can be used in addition to the well known 51Cr-release assay. Also, since the mouse spleen cell is a normal cell, it provides a model in the PFC system for studying the mechanism of NK regulation of normal cellular function. An additional finding of this study was the observation that E-rosetting T cells significantly enhanced the mouse PFC response. Thus, human peripheral lymphocytes contain discrete cellular populations that either enhance or suppress the mouse PFC response. (Author abstract) (19 Refs)

124. PERSPECTIVES OF LYMPHOCYTE PRODUCTION AND CELLULAR TRAFFIC IN THE BONE MARROW.

Rosse C
Dept. Biological Structures, Univ. Washington Sch. Medicine, Seattle, WA, 98145
The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

A review is presented of the magnitude of lymphocyte production in bone marrow (BM) and the heterogeneity of lymphocytes produced in BM. The following areas are discussed: population size and turnover rate of bone lymphocytes; generation of B lymphocytes in BM; T cells and T cell precursors in BM; immunocompetence of BM T cell precursors; regulatory role of BM lymphocytes; and role of BM in antitumor responses. (179 Refs)

125. GENERATION OF CYTOTOXIC LYMPHOCYTES BY SV40-INDUCED ANTIGENS.

Chang C, Chang R, Mora PT, Hu C
Dept. Medical Res., Veterans General Hosp., Taipei, Taiwan, Republic of China
J Immunol; 128(5):2160-2163 1982

In order to study the correlation of in vivo tumor transplantation immunity and in vitro immunologic assays, cell-mediated cytotoxicity against SV40-transformed cells was studied in AL/N strain mice by using 51Cr-release assay. Killing of SV40-transformed AL/N fibroblast cells was observed by spleen cells of AL/N mice immunized with syngeneic SV40-transformed cells. Immunization with the solubilized SV40 tumor-specific transplantation antigen (TSTA) that induced transplantation immunity in vivo did not elicit cytotoxic spleen cells in vitro. However, the spleen cells from mice immunized with solubilized TSTA and then sensitized in vitro with SV40-transformed cells became cytotoxic against SV40-transformed fibroblasts. Similarly, SV40 TSTA (T antigen) purified by immunoprecipitation was able to prime the lymphocytes in AL/N mice: the primed lymphocytes could differentiate into cytotoxic lymphocytes upon in vitro stimulation by SV40-transformed cells. These data indicate that SV40 TSTA (T antigen) plays a role in the induction of cytotoxic lymphocytes. (Author abstract) (30 Refs)

126. TG CELL INVOLVEMENT IN THE LEUKOCYTE ADHERENCE INHIBITION PHENOMENON.

Taylor SG, Saffold PC, Braun DP, Harris JE
Section Medical Oncology, Dept. Internal Medicine, Rush-Presbyterian-St. Luke's Medical Center, 1725 West Harrison St., Chicago, IL, 60612
JNCI; 68(4):549-554 1982

Peripheral blood mononuclear cells (PBMC), T-cells, non-T-cells, TG cells, and TM cells were tested for leukocyte adherence inhibition (LAI) reactivity to purified protein derivative (PPD) in normal human volunteers to determine the reactive cell subfractions. T-cells were separated by sheep red blood cell rosetting and TM and TG cells by rosetting with anti-ox red blood cell (ORBC) IgM- and IgG-treated ORBC. Fresh

PBMC, T-cells, and TG cells gave positive LAI reactivity to PPD in PPD-positive donors only. PBMC that had undergone 24-hr incubation or extensive washing, non-T-cells, and TM cells were unreactive. All cell subfractions were negative in PPD-negative donors. Indirect LAI assay was performed on the spent media from overnight incubation of unstimulated PBMC and also following a 1-hr incubation of the various cell subfractions obtained from a PPD-reactive donor with PPD. Positive reactions, indicating the release of an LAI factor (LAIF), were obtained with the spent media and with the T-cell and TG cell subfractions following PPD stimulation, whereas non-T-cell and TM cell subfractions yielded no reactivity. Incubation of sensitized T-cells with PPD in the presence of cycloheximide and preincubation of T-cells for 24 hr with cycloheximide before PPD exposure failed to inhibit LAI reactivity. These data suggest that T-cells, specifically TG cells, can release LAIF upon specific antigen stimulation with PPD, whereas non-T-cell and TM cell subpopulations fail to respond to the same stimulus. LAIF may also be released into the culture media with prolonged (overnight) incubation in artificial media or with extensive washing. Inhibition of protein synthesis during antigen exposure or up to 24 hr before antigen exposure does not appear to inhibit LAI reactivity. (Author abstract) (27 Refs)

127. CELL-MEDIATED CYTOTOXICITY TO NON-MHC ALLOANTIGENS ON MOUSE EPIDERMAL CELLS. IV. AN ALLOANTIGEN SHARED WITH B CELLS BUT NOT T CELLS.

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Cell Immunol; 68(1):93-103 1982

Cytotoxic T lymphocytes raised by immunization of C3H with AKR epidermal cells (EC) strongly cross-react with AKR lymphocyte (LC) targets, provided the LC are cultured prior to use as target cells. By nylon-wool separation, negative-selection, positive-selection, and cold-target inhibition methods, we have identified B cells as the susceptible LC targets and determined that their antigenicity requires a culture-induced, proliferation-independent change in antigen expression. Questions concerning the nature of the culture-induced event, the identity of the B-cell alloantigen, and its concomitant expression by EC are discussed. (Author abstract) (15 Refs)

128. HUMAN T CELL SUBCLASSES WITH IGG AND COMPLEMENT RECEPTORS.

Chiao JW

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The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

Studies on the nature of T lymphocytes possessing both commonly used markers (IgG or complement) and once referred to as cells having both B and T markers, now considered T-lymphocyte subclasses, are presented. Topics include tissue distribution and presence in lymphoid neoplasms, functional properties (antibody dependent cellular-cytotoxicity), suppressor and helper cell functions, activated T cells, and mitogenic responses and other functions. Cell morphology and the development of T cell subclasses are discussed. (160 Refs)

129. FUNCTIONAL STIMULATION OF T CELLS WITH PROTEIN ANTIGENS.

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Dept. Bacteriology and Immunology, Univ. Helsinki, 00290 Helsinki 29, Finland

The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

The triggering requirements of various T cells, the interactions between different T cells in immune regulation, and functions of actual effector cells are discussed. Areas discussed include cells participating in immune responses (B and T lymphocytes, accessory cells [macrophages]); stimulation of T cells (processing of antigen [Ag], Ia antigens on Ag presenting macrophages, role of I region genes); functional assays of T cell stimulation (T cell proliferation and cytotoxicity, delayed hypersensitivity); antibody production (T cell help, T cell suppression); T cell derived mediator molecules (mice, humans); and new approaches for the characterization of specific T cell mediator molecules. (157 Refs)

130. T-CELL DEPLETION OF ALLOGENIC MLR-INCOMPATIBLE MARROW RESULTS IN SUCCESSFUL TRANSPLANTATION WITHOUT GRAFT VS HOST DISEASE (GVHD) (MEETING ABSTRACT)

Ozer H, Higby DJ, Brass C, Marinello M, Han T

Roswell Park Memorial Institute, Buffalo, NY, 14263

Proc Am Soc Clin Oncol; 1:C-724 1982

GVHD following marrow transplantation is more probable and of greater severity when donor and recipient are incompatible at the HLA, DR, or mixed leukocyte culture (MLC) loci. GVHD is mediated by T cells which contaminate harvested marrow in varying proportions. T cell depletion (TCD) of large volumes of human marrow by E-rosetting for 24 hr at 4 C with modified sheep erythrocytes was employed to achieve removal of greater than 99% of T cells. In two patients in whom donor and recipient were HLA-A and B identical but MLR (mixed leukocyte reaction) reactions were strongly positive, donor marrow subjected to TCD successfully engrafted without GVHD. EB, a 26 y/o male with severe aplastic anemia received cyclophosphamide conditioning followed by infusion of 8.4 x 10(8) colony forming units in culture (CFUc) of TCD marrow. His recovery course was complicated only by fever and granulocyte count returned to 1000 mm3 34 days later. He is asymptomatic with a normal marrow 7 months post transplant. DH, a 23 y/o female with refractory acute myelocytic leukemia, received conditioning with high-dose ARA-C (cytosine arabinoside), cyclophosphamide and total body irradiation, followed by infusion of 3.7 x 10(8) CFUc (colony forming unit culture)) of TCD marrow. Invasive oropharyngeal candidiasis and staphylococcus epidermidis bacteremia, but not GVHD, complicated her course, and granulocyte count reached 1000/mmm3 28 days post transplant. At 53 days, her marrow is normal and cytogenetics confirm chimerism. In contrast, 22/26 HLA and MLC identical allogeneic marrow transplants performed without TCD had evidence of GVHD. Marrow grafts depleted of T cells in the mismatched setting can restore durable hematopiesis while reducing or eliminating GVHD. (no Refs)

131. THE HANDBOOK OF CANCER IMMUNOLOGY. VOLUME 6: LYMPHOID CELL SUBPOPULATIONS: STRUCTURE, FUNCTION, AND INTERACTIONS.

Waters H
NIH, Bethesda, MD
The Handbook of Cancer Immunology. Volume 6: Lymphoid Cell Subpopulations: Structure, Function, and Interactions. New York, Garland STPM Press, 314 pp., 1981.

Lymphoid cell subpopulations are discussed in relation to cellular interactions in metastasis, role of immunosuppressants in lymphocyte function, human T cell subclasses with IgG and complement receptors, age-related changes in marrow stem cells, functions of atypical lymphocytes, biology of marrow-dependent cells in mice, pathogenesis of plasma cell tumors, functional stimulation of T cells with protein antigens, effects of lymphokines on tumor cells, and perspectives of lymphocyte production and cellular traffic in the bone marrow. (1334 Refs)

132. AGE RELATED CHANGES IN MARROW STEM CELLS.

Tyan ML
Medical and Res. Services, Veterans Admin., Wadsworth Medical Center, Los Angeles, CA, 90073
The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

Origins and maturation of the immune system and other marrow cells with which it interacts are described, based chiefly on studies in the mouse. The monocyte-macrophage and two classes of lymphocytes, B and T cells, have been shown to participate specifically in the afferent and efferent arms of the immune responses, but discussion is limited to lymphocytes and macrophages and to the marrow hematopoietic stem cells (CFUs) with which they interact. (124 Refs)

133. THE BIOLOGY OF MARROW DEPENDENT CELLS IN MICE.

Kumar V, Bennett M
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The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

After 89Sr administration in mice, certain effector functions such as marrow allograft reactivity, genetic resistance against Friend virus leukemia, and natural killer (NK) activity are lost. Such effector functions may be mediated by a distinct class of immunocompetent cells which are critically dependent on the bone marrow microenvironment (M cells) for differentiation. These M cells may be NK cells. The relationship between NK cells and other effector functions of M cells, and the regulatory function of M cells, are discussed. (41 Refs)

CMI METHODOLOGY

134. HLA ANTIGEN EXPRESSION ON UROTHELIAL CELLS: DETECTION BY ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY.

O'Toole CM, Tiptaft RC, Stevens A
Div. Immunology, Addenbrooke's Hosp., Laboratories Block, Hills Road, Cambridge, CB2 2QQ, England
Int J Cancer; 29(4):391-395 1982

Antibody-dependent cell-mediated cytotoxicity (ADCC) was used to detect HLA-A, -B and -C antigens on in vitro-cultured urothelial cells of normal or malignant derivation. Alloantisera induced specific lysis of 51Cr-labeled targets by effector lymphoid cells from non-immune donors. HLA antisera were routinely titered to dilutions greater than or equal to 10(-3) on urothelial cells in primary or long-term culture. The HLA phenotype was compared for lymphoid cells and urothelial cells from eight individuals. HLA antigens detected by complement mediated lymphocytotoxicity were also detected on urothelial cells. No deletions or gains in HLA antigens were found on normal or malignant urothelial cultures as compared with donor lymphocyte HLA typing. The results show that the established urothelial cell lines J82, TCCSuP and SCaBER have retained their donor HLA phenotype. The established cell lines T24 and RT4 derived from transitional cell carcinomas and HCV-29 from urothelium were found to have distinctive HLA profiles although donor lymphocytes were not available for comparison. The serological crossreactions seen in complement mediated lymphocytotoxicity were clearly observed in ADCC. In particular, HLA-Cw5 was found to crossreact with HLA-Cw8. HLA-Cw5 was detected on 6/8 cultures of transitional cell carcinomas and this was confirmed by absorption analysis. (Author abstract) (19 Refs)

135. STUDIES ON SUPEROXIDE PRODUCTION OF HUMAN NEUTROPHILS PART 1. EXPERIMENTAL STUDIES ON SUPEROXIDE PRODUCTION OF HUMAN NEUTROPHILS.

Kohi F

Dept. Internal Medicine, Okayama Univ. Medical Sch., Okayama 700, Japan

Okayama Igakkai Zasshi; 93(9/10):873-883 1981

Patients with acute leukemia are prone to get infections. Pathological conditions such as leukocytopenia and disturbances of humoral and cellular immunity are thought to contribute to this. Superoxide, one of the active oxygens, is thought to be related to the intracellular bactericidal activities of neutrophils, particularly in oxygen dependent systems. These findings led to speculations that primary and secondary disturbances in the superoxide production of neutrophils are of importance in the high susceptibility of patients with acute leukemia. In this experiment, the superoxide production of normal human neutrophils stimulated by Concanavalin A and Cytochalasin D was assayed by spectrophotometery in order to evaluate its usefulness in clinical applications. The effect of age and sex on superoxide production was also examined. The following results were obtained: (1) The activity of superoxide production was affected by both time and temperature during cell preservation. It was also dependent on the cell concentration, temperature and pH during stimulation of the neutrophils. The optimal system for assay of the superoxide production of human neutrophils was as follows: Cells should be preserved at 0 C within 60 min. During stimulation, cell concentration, temperature and pH should be adjusted to 0.2-0.5 X 10(6)/ml, 37 C and 7.4, respectively. (2) There were no significant changes in superoxide production between males and females. Superoxide production in older subjects was significantly lower than that in younger subjects. Assays of superoxide production of human neutrophils can be clinically used because of its simplicity and reproducibility. It was apparent that the assessment of superoxide production of neutrophils by age was necessary in clinical applications. (65 Refs) (In JPN)

136. LECTIN-DEPENDENT CELL-MEDIATED CYTOTOXICITY. A NEW AND SIMPLE METHOD TO QUANTITATE CYTOTOXIC T CELL ACTIVITY IN DOGS.

Emeson EE, Norin AJ, Veith FJ
Dept. Pathology, Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, NY, 10467
Transplantation; 33(4):365-369 1982

Alloimmune T lymphocytes kill a wide spectrum of target cells, even in the absence of alloantigen recognition, providing that a lectin is incorporated into the assay medium. In these studies we have modified the lectin-dependent cell-mediated cytotoxicity (LDCMC) assay to evaluate the cytotoxic activity of canine T cells using a human B lymphoblastoid cell line (Raji) as the target. Canine peripheral blood mononuclear cells activated in vitro in mixed leukocyte cultures or by concanavalin A (Con A) killed 51Cr-labeled Raji target cells (up to 70% in 4 hr) when Con A was included in the assay. T cells expressed cytotoxic activity only when activated and when Con A was present in the assay. Canine T cells activated in vivo also exerted cytotoxic activity in the LDCMC assay. T cells obtained from a rejecting allografted lung by bronchoalveolar lavage displayed considerably higher cytotoxic activity than did T cells obtained from the contralateral normal lung or peripheral blood of the same dog. In contrast, T cells from the lungs and blood of normal dogs and lung-allografted dogs without rejection exerted no cytotoxic activity. We conclude that the LDCMC assay using xenogeneic Raji cells as targets is a valid measure of the cytotoxic activity of canine T cells. Its major advantages include the fact that it is simple to perform and can be used when specific target cells are not available. (Author abstract) (28 Refs)

SUPPRESSOR CELL ACTIVITY

137. GENERATION OF SUPPRESSOR CELLS FOR NATURAL KILLER ACTIVITY IN CANCER PATIENTS AFTER SURGERY.

Uchida A, Kolb R, Micksche M
Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Vienna, Austria
JNCI; 68(5):735-741 1982

Natural killer (NK) cell activity was examined in breast cancer patients before and after surgery, and the cells involved in the postoperative depression of cytotoxicity were characterized. NK activity against K562 target cells determined in a 4-hour 51CR release assay of blood lymphocytes from preoperative patients was comparable to that of normal donors. After surgery the patients showed a decrease in NK activity but not in number of large granular lymphocytes in the effector cell populations. When blood mononuclear cells from postoperative patients were depleted of monocytes by adherence to a serum-coated plastic dish and a Sephadex G10 column and then cultured for 24 hours, they showed an increase in NK activity. Furthermore, adherent blood cells of postoperative patients, but not of normal donors or preoperative patients, suppressed the lytic function of NK cells of normal individuals. Twenty-four-hour preculture of suppressor and effector cells was required for suppression of cytotoxicity. Neither postoperative sera nor culture supernatants of suppressor monocytes and effector cells suppressed NK activity. In contrast, the lymphoproliferative response to mitogen was not affected by surgery, and postoperative blood monocytes did not inhibit the mitogenic response of normal lymphocytes. The results suggest that the appearance of suppressor monocytes in the circulation could be one cause of depression of NK activity in postoperative cancer patients. (Author abstract) (41 Refs)

138. A PARTIAL CHARACTERIZATION OF SUPPRESSOR CELLS IN RAT FETAL LIVER CELLS.

Monden M, Staruch AJ, Fortner JG
Dept. Surgery, Osaka Univ. Medical Sch., Fukushima-Ku, Osaka 553, Japan
Cell Immunol; 68(1):16-24 1982

Rat fetal liver cells (FLC) obtained at 18-20 days gestation suppressed mixed lymphocyte reactions (MLR) of adult lymph node cells. The suppression was not strain specific: both syngeneic and allogeneic FLC were capable of suppressing the MLR. The same suppressor activity was observed with fetal spleen cells but not with fetal thymus cells. Removal of phagocytic cells from FLC failed to inhibit the suppressor activity. The suppressor cells were separated into two different types by BSA density gradient: one is radiosensitive, the other radioresistant. A stronger suppressor activity was observed in radiosensitive cells. The suppressor cells belonged to the fraction agglutinated with peanut agglutinin. The data suggest that the suppressor cells in rat FLC may be a proliferating blastoid-type cell rather than mature lymphocytes or mature macrophages. (Author abstract) (27 Refs)

139. PARTIAL RESTORATION OF LOCAL GVH REACTION IN CANCER PATIENTS BY DEPLETION OF THEOPHYLLINE-SENSITIVE SUPPRESSOR T-CELLS.

Mavligit GM, Wong WL
Developmental Therapeutics, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(10):2029-2033 1982

Theophylline-resistant T-cell subpopulations were assessed in terms of numbers and function among patients with disseminated cancer, and compared to normal controls. Within the total E-rosetting T-cells (65 +-6.5% for normal donors vs 34 +-1.0% for cancer patients; p less than 0.001) the proportion of theophylline-resistant Te-cells was 56 +-1.5% and 26.6 +-1.1%, respectively (p less than 0.001). This significant difference in distribution between theophylline-resistant (effector) and theophylline-sensitive (suppressor) cells in favor of the latter was also reflected by the poor performance of unseparated T-cells in the local GVH reaction. Thus, the mean GVH reaction among normal donors was 159 +-30 mm3 vs 44 +-28 mm3 among cancer patients (p less than 0.001). Removal of the theophylline-sensitive suppressor T-cells resulted in significant augmentation of the local GVH reaction among normal donors and in significant, although partial, immune restoration of the local GVH reaction in some patients but not in others. The mean local GVH reaction after removal of theophylline-sensitive suppressor T-cells was 196 +-89 mm3 among normal donors and 68 +-46 mm3 among cancer patients (p less than 0.05). This immune restoration following depletion of suppressor T-cells was only partial among cancer patients because of an apparent intrinsic defect in the capacity of their effector T-cells to exert vigorous local GVH reaction. In one small group of four patients, this intrinsic defect was so profound that even after removal of the theophylline-sensitive suppressor cells, the restoration of the local GVH reaction was negligible (12 +-10.8 mm3 vs 24 +-9.8 mm3; p greater than 0.1). The quantitative and qualitative changes in effector and suppressor T-cell distribution during the development of the malignant process and the possible interaction between them are discussed. (Author abstract) (27 Refs)

140. INDUCTION OF INDOMETHACIN SENSITIVE SUPPRESSOR CELLS (ISSC) BY CORYNEBACTERIUM PARVUM (C. PARVUM) AND THE EFFECT OF INTERLEUKIN-2 (IL-2) (MEETING ABSTRACT)

Maca R
Veterans Administration Center and Louisiana State University Medical, Center Shreveport, LA, 71130
Proc Am Assoc Cancer Res; 23:957 1982

Studies were designed to determine whether increased prostaglandin production by these cells could account for this suppressed state. C parvum was injected IP or IV into C57BL/6 mice. After various intervals, the mice were sacrified, spleen cell suspension prepared and incubated with concanavalin A (Con A) with or without indomethacin (indo), an inhibitor of prostaglandin synthesis. In duplicate cultures, IL-2 was added. After 72 hours of incubation, the cultures, which were pulsed with 3H-thymidine, were harvested, radioactivity counted and % augmentation by indo or IL-2 calculated. Five to 7 days after IP injection of 350 ug C parvum, the reactivity of the spleen cells average 65.3 x 10(3) cpm/well which was augmented 77.9% by indo, as compared to control values of 104.9 x 10(3) cpm/well and 19.4% respectively. Significant augmentation by indo was seen by day 3, persisted past day 14 and was apparent with as little as 50 ug C parvum. When given IV, this agent was also effective in inducing suppression of Con A reactivity, averaging 39.5 x cpm/well, which was likewise enhanced by 91.4% by indo. When IL-2 was added simultaneously with indo, a further increase in Con A reactivity, averaging 30.1%, was seen. Often depressed proliferative responses were normalized by this combination. (no Refs)

141. LOSS OF THE SHORT LIVED SUPPRESSIVE FUNCTION OF PERIPHERAL LEUKOCYTES IN FELINE RETROVIRUS-INFECTED CATS (MEETING ABSTRACT)

Stiff MI, Olsen RG
Department of Veterinary Pathobiology, Ohio State University, 1925 Coffey Road, Columbus, OH, 43210
Proc Am Assoc Cancer Res; 23:1097 1982

This research examined the short-lived suppressive function of normal and retrovirus-infected (FeLV, feline leukemia virus) cat peripheral blood mononuclear cells (PBMC). Normal specific-pathogen-free cats (SPF) demonstrated an increased lymphocyte blast transformation (LBT) with a suboptimal amount of concanavalin A (con A, 0.1 ug/10(5) PBMC) after a 24 hour delay in mitogen addition as compared to 0 hour mitogenesis. The suppressive removal index (SRI) was calculated by a delta 24 hour mitogenesis /delta 0 hour mitogenesis. Increased stimulation after 24 hours which was not due to enhancing factors accumulating in the culture medium has been attributed to a short-lived suppressor cell function. The average SRI for normal SPF cats was 3.8. This phenomenon was subsequently studied in retrovirus-infected (FeLV) cats who demonstrated a loss of this function with an average SRI of 1.1 which was significantly lower than uninfected animals. This lower index was a result of a higher 0 hour mitogenesis. Therefore, this data suggests a loss of suppressor function during the viremic stages of feline leukemia which may be due to an overall immunosuppression of cellular immune functions including suppressor cells. Ultimately loss of suppressor cells may contribute to the findings of a Coomb's positive anemia associated with feline leukemia pathogenesis. (no Refs)

142. ACTIVATION OF A SUPPRESSOR CELL PATHWAY BY HUMAN LEUKOCYTE INTERFERON (MEETING ABSTRACT)

Schnaper HW, Aune TM, Pierce CW
Jewish Hospital of St. Louis, St. Louis, MO, 63110
Fed Proc; 41(3):442 1982

Murine interferon activates suppressor T cells which produce soluble immune response suppressor (SIRS), a lymphokine that inhibits responses by murine lymphoid cells. We investigated whether human leukocyte interferon (IFNalpha) acts by a similar mechanism. Human peripheral blood mononuclear cells (PBMC) were stimulated with pokeweed mitogen and assayed for polyclonal plaque-forming cell (PFC) responses. IFNalphaA suppressed PFC responses approx 90% at doses greater than 100 units/culture. No suppression was observed in the first 5 days; suppression was maximum on days 7 and 8. This delayed suppresson suggested that IFNalphaA may activate a suppressor cells. PBMC were incubated with IFNalphaA for 24 hrs and added at initiation to cultures of PBMC from the same individual. Small numbers of IFNalphaA-activated cells suppressed responses by 80% compared to cells incubated with inactive IFNalphaA. Suppression was delayed and maximal on day 7. IFNalphaA and IFNalphaA-activated cells did not suppress responses in the presence of catalase or 2-mercaptoethanol (2-ME). The delayed onset of suppression, activation of a suppressor cell and reversal of suppression by catalase and 2-ME suggest that human IFNalphaA activates a suppressor pathway analogous to that activated by interferon in murine cells and suggests that a SIRS-like mediator may be involved. (no Refs)

143. SELECTIVE IMPAIRMENT OF SUPPRESSOR T CELL FUNCTION AFTER ADMINISTRATION OF CYCLOPHOSPHAMIDE (CY) (MEETING ABSTRACT)

Berd D, Danna V, Maguire H, Mastrangelo MJ
The Fox Chase Cancer Center, Philadelphia, PA, 19111
Proc Am Assoc Cancer Res; 23:1104 1982

Administration of CY to patients with metastatic cancer 3 d prior to immunization with antigen augments the delayed type hypersensitivity (DTH) response to that antigen. To explain this finding, we collected peripheral blood lymphocytes (PBL) from patients with metastatic melanoma before and after (1, 2, 3, 7, 14, and 21 d) CY 1000 mg/M2 IV. PBL were frozen, and all samples from a patient were thawed and tested on the same day. We performed PBL counts, analyzed the composition of PBL with a panel of fluoresceinated monoclonal antibodies and a cell sorter, measured their response to phytohemagglutinin (PHA) and pokeweed mitogen (PWM), and tested their ability to generate concanavalin A (Con A) suppressor cells. The PBL count decreased by a mean of 34.8% at 2 d and remained depressed through 21 d. There was no significant change in the relative proportions of B cells (Ig+), T cells (Leu 1+), or the helper-inducer (Leu 3+) or suppressor-cytotoxic (Leu 2+) subsets of T cells. In contrast, there was a change in the function of PBL after CY. Thus, 3 d and 7 d after CY, the ability to generate suppressor T cells was diminished, while the response to PHA and PWM, dependent on helper T cells, had recovered. This selective impairment of suppressor function could explain the immunopotentiating effect of CY in these patients. (1 Ref)

144. INTERFERON INHIBITS THE SUPPRESSOR T-CELL RESPONSE OF DELAYED-TYPE HYPERSENSITIVITY.

Knop J, Stremmer R, Neumann C, DeMaeyer E, Macher E
Hautklinik der Universitat Munster, von-Esmarch-Strasse 56, D-4400 Munster, W. Germany
Nature; 296(5859):757-759 1982

The effect of an electrophoretically purified mouse interferon (IFN-alpha and IFN-beta) preparation on the suppressor T lymphocyte (TS) response to dinitrofluorobenzene was examined in BALB/c mice. In vitro treatment of TS with interferon revealed a subpopulation of immune regulatory lymphocytes highly sensitive to interferon (1 U of interferon inhibited TS cells present in 10(5) spleen lymphocytes). Iv injection of 1,000 U of the interferon preparation inhibited the function of TS in recipient animals when given 2 hr after transfer of the TS and after incubation of spleen cells from tolerant animals with interferon before transfer into recipients. The T effector lymphocytes of delayed-type hypersensitivity (TDH) response was not affected by the same amount of interferon. (17 Refs)

OTHER RELATED STUDIES

145. EXPRESSION OF HLA ANTIGENS ON LEUKEMIA CELLS.

Mayer S, Tongio MM, Falkenrodt A, Pfeiffer B, Bergerat JP
Institut d'Hematologie, Centre de Transfusion Sanguine, 10, rue Spielmann, 67085 Strasbourg Cedex, France
J Immunogenet; 9(2):111-120 1982

HLA antigens of 10 leukemic cell lines were investigated using an absorption method and the results were compared with those of normal lymphocytes. Cell lines from five patients with acute myeloblastic leukemia, one with acute lymphocytic leukemia, two with blastic lymphomas, one with acute myelomonocytic leukemia, and one with chronic granulocytic leukemia in an acute lymphoblastic crisis were used. The number of pathological cells exceeded 80% in seven patients and 60% in three. A detailed leukocyte count is presented. Anti-B5, anti-B7, and anti-B12 sera were absorbed on the healthy lymphocytes and the 10 leukemia cell lines and the residual cytotoxicity is illustrated. For anti-A1 + B8 and anti-A2 sera, only leukemia cells were used for absorption. Leukemia cells absorbed anti-HLA antibodies as effectively as healthy lymphocytes when the cells carried the antigen corresponding to the serum specificity. The curves obtained with leukemia cells were comparable to those of healthy cells. Leukemia cells were also capable of absorbing antibodies when the cells were not carriers of the antigen corresponding to the antibody's specificity. Only a few types of healthy lymphocytes were capable of weak absorption of anti-HLA sera. In most cases, 500 leukemic cells were sufficient to absorb anti-HLA sera and the absorption usually increased with the number of cells used. This 'non-specific' absorption was poorer than that noted with cells carrying the antigen corresponding to the antibody. In most cases, nonspecific absorptions could not be explained by cross-reactions. (11 Refs)

146. SERO-EPIDEMIOLOGIC STUDIES ASSOCIATE THE HUMAN T-CELL LEUKEMIA-LYMPHOMA VIRUS (HTLV) WITH ADULT MALIGNANCY OF MATURE T-CELLS (MEETING ABSTRACT)

Robert-Guroff M, Kalyanaraman VS, Sliski A, Blattner W, Catovsky D, Sarngadharan MG, Gallo RC
Litton Bionetics, Inc., Kensington, MD, 20895
Fed Proc; 41(3):689 1982

HTLV, a unique human retrovirus (RNA tumor virus), was isolated from cells of patients with lymphomas and leukemias of mature T-cells. Surveys of sera for antibodies to HTLV have shown HTLV to be rarely associated with such diseases in the US, but strongly linked to Japanese adult T-cell leukemia (ATL), lymphosarcoma T-cell leukemia (LCL), and peripheral T-cell lymphoma. LCL is a malignancy of mature T-cells seen in some Caribbeans. ATL is a similar disease clustered geographically in Southwest Japan. Sera of 19 of 22 ATL patients and 3 of 3 LCL patients had antibodies to HTLV p24 and p19 as determined by radioimmunoprecipitation of p24 or by competition radioimmunoassay with a monoclonal anti-p19. Among sera of relatives of sero-positive patients, 20% were also positive, supporting the infectious nature of HTLV. Other normal donors lacked antibodies to HTLV, except for some healthy Japanese in the ATL endemic area, suggesting widespread viral exposure. Sera of children in the US with leukemias, lymphomas, and solid tumors were negative, as were sera from numerous adults with various neoplasias. While HTLV is thus not prevalent in this country, it may play a role in the etiology of mature T-cell neoplasias in other geographic locales. (no Refs)

147. MECHANISMS OF INHIBITION OF MOUSE MYELOID LEUKEMIC CELL DIFFERENTIATION BY PROSTAGLANDIN F2ALPHA.

Takenaga K, Honma Y, Kado J, Hozumi M
(c/o Hozumi) Dept. Chemotherapy, Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-ken 362, Japan
Gan; 73(2):175-183 1982

Mouse myeloid leukemia M1 cells were induced to differentiate in vitro into macrophages and granulocytes by various inducers, including dexamethasone. Prostaglandin F2alpha inhibited the inductions by dexamethasone of phagocytic and lysozyme activities in M1 cells. Prostaglandin F2alpha stimulated the production of differentiation-inhibiting activity (I-activity) in M1 cells. I-activity production by prostaglandin F2alpha was decreased by simultaneous treatment with actinomycin D (5 ng/ml) but not with 5-fluoro-2'-deoxyuridine (10 ng/ml). The I-activity was inactivated by heating (70 C, 20 min) or by treatment with trypsin but not with mixed glycosidases or ribonuclease, suggesting that I-activity was due to a proteinous substance(s). B-Type prostaglandins also stimulated I-activity production, whereas A-, E- and D-type ones did not. Induction of I-activity by prostaglandin F2alpha was suppressed by simultaneous treatment with prostaglandin E2. Retinoic acid stimulated the synthesis and release of prostaglandin F2alpha and production of I-activity in M1 cells. Indomethacin completely inhibited induction of I-activity by retinoic acid. On the basis of these result, the relationship between I-activity production and prostaglandin F2alpha production is discussed. (Author abstract) (39 Refs)

148. A CASE OF ACUTE LYMPHOBLASTIC LEUKEMIA WITH PRE-B CELL CHARACTERISTICS.

Sugita K, Iwama Y, Mizushima W, Kato K, Umino T, Eguchi M, Furukawa T
The Second Dept. Pediatrics, Dokkyo Univ. Sch. Medicine, Japan
Rinsho Ketsueki; 22(12):1994-2000 1981

A case of pre-B cell acute lymphocytic leukemia (pre-B cell ALL) with various symptoms in addition to abnormal karyotype is reported. The patient was a 6-yr-old girl who complained of fever and swollen face; enlargement of lymph nodes and weak breathing in the left chest were noted. Tests revealed a decrease in platelets and a marked increase in leukocytes in which 81% were abnormal blast cells. The ratio of T cells to B cells was 6:1. Abnormal blast cells occupied 99.4% of the bone marrow. Abnormal karyotype (46XX, 8-, 11-, m+1, m+2) was found in chromosome analysis. Complete remission lasting 3 mo was obtained with vincristine (VCR), prednisolone, and L-asparaginase. Further treatment included methotrexate, VCR, cytosine arabinoside, and adriamycin; only partial remission and clinical improvement were obtained. The patient survives 18 mo from the start of treatment. (14 Refs) (In JPN)

149. THE PATHOGENESIS OF PLASMA CELL TUMORS.

Hollander VP, Platica M
Res. Inst., Hospital for Joint Diseases, New York, NY, 10035
The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

The possibility is examined that common factors are at play in the mineral-oil induced plasma cell tumors (PCT) in BALB/c mice because so many endocrine factors appear to modulate tumorigenesis. The working hypothesis involves bacterial lipopolysaccharide in a transformation step, pristane-induced peritoneal factors in the successful adaptation of nascent tumor cells to the host, and finally, an immunosuppression step which permits rapid growth. Hormones are involved in the earlier steps of plasmacytoma development. (145 Refs)

150. 1-BUTANOL EXTRACTION AND SUBSEQUENT RECONSTITUTION OF MEMBRANE COMPONENTS WHICH MEDIATE METASTATIC PHENOTYPE.

LeGrue SJ
Dept. Surgery, Div. Immunology and Organ Transplantation, Univ. Texas Medical Sch., Houston, TX, 77030
Cancer Res; 42(6):2126-2134 1982

The purpose of this study was to examine the effect of noncytolytic 1-butanol extraction of cell membrane components upon the metastatic potential of iv injected neoplastic cells. Butanol extraction consistently increased the number of pulmonary, but not extrapulmonary, lesions observed following challenge of (a) C3H/HeJ mice with the chemically induced fibrosarcoma MCA-F or (b) C57BL/6J mice with the spontaneous melanoma B16. Variants of these cell lines which display either a low (MCA-F parental and B16-F1) or a high (MCA-F 9.4 and B16-F10) proclivity to induce pulmonary metastases were all affected by pretreatment with butanol. Organ distribution studies using 5-[125I]iododeoxyuridine-labeled B16-F10 cells demonstrated that significantly more butanol-extracted cells were initially arrested in the lungs but that the number of extracted and control cells in the pulmonary bed equalized over the first 3 hr. During the next 7 days, butanol-extracted cells were preferentially retained in the lungs, resulting in a 3-to 4-fold increase in the number of macroscopic pulmonary foci observed 3 wk later. The enhanced initial arrest of extracted cells was not mediated by increased tumor cell homoaggregation or by tumor cell:lymphocyte heteroaggregation, nor did butanol extraction select cells with an intrinsically greater metastatic potential. However, the preferential survival of extracted cells may result from an increased resistance to natural cell-mediated cytotoxicity, since (a) pretreatment of hosts with a copolymer of polyinosinic and polycytidylic acids prior to challenge with extracted cells profoundly decreased the number of lung colonies, and (b) butanol extraction of YAC-1 lymphoma target cells decreased the ability of C57BL/6J splenocytes to effect natural cell-mediated cytotoxicity in an in vitro 51Cr release assay. Finally, reassociation of the extracted moieties with the membranes of butanol-extracted cells resulted in the constitution of the original metastatic phenotype. These results suggest that cell surface structures which mediate the successful establishment of pulmonary metastases are reversibly released by brief incubation of cells in aqueous solutions of 1-butanol. (Author abstract) (37 Refs)

151. THE RELATIONSHIPS BETWEEN ENZYME INHIBITORS AND FUNCTION OF MAMMALIAN CELLS.

Aoyagi T, Umezawa H
Inst. Microbial Chemistry, 14-23 Kamiosaki 3-Chome, Shinagawa-ku, Tokyo 141, Japan
Acta Biol Med Ger; 40(10/11):1523-1529 1981

Enzyme inhibitors, increased enzyme activities in some diseases, and possible application of inhibitors in the treatment are discussed. Enzyme inhibitors found in culture filtrates of microbes are leupeptin, antipain, chymostatin, elastatinal, pepstatin, hydroxypepstatin, pepstanone, and phosphoramidon. They inhibit serine protease, thiol protease, carboxyl protease, and metallo protease. The activities of aminopeptidase, alkaline phosphatase, and esterase were observed on the surface of lymphocytes, macrophages, normal or virus transformed cells, and tumor cells. Searching for specific inhibitors against these cell surface enzymes, inhibitors such as bestatin, amastatin, forphenicine, esterastin, ebelactone A, and ebenlactone B were discovered. Bestatin enhances the production of Type II interferon in phytohemagglutinin- or concanavalin A-stimulated mouse spleen cells. Bestatin inhibits the growth of Gardner lymphosarcoma and IMC carcinoma, and enhances the therapeutic effect of antitumor agents such as adriamycin and bleomycin. Bestatin increases the number of granulocytes in bone marrow both in vitro and in vivo. In clinical studies of cancer treatment, the decrease in number of T-cells was reversed by daily administration of 10-100 mg bestatin po. Bestatin reversed the decrease in NK cell activity in cancer patients. Activities of various enzymes were measured in relation to disease processes and the effect of the inhibitors on the enzyme activities was studied. Various enzyme activities in synovial fluids of patients with osteoarthritis and rheumatoid arthritis are presented. (13 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abe O 81
Abebe A 41
Ablin RJ 7
Adams DO 106
Adler WH 57
Adorjan I 41
Akimova GV 23
Akiyama Y 80
Allavena P 105
Allavena P 16
Ames RS 73
Amouroux J 39
Aoki T 19
Aoki T 20
Aoki T 72
Aoki T 80
Aoyagi T 151
Arai S 84
Aune TM 142
Babakova SV 5
Bachner R 31
Bailargeon LM 52
Baines MG 15
Banti G 7
Bartlett GL 43
Bast RC 11
Battesti JP 39
Bekesi JG 24
Benacerraf B 96
Bennett M 133
Beppu Y 121
Berd D 143
Berek JS 11
Bergerat JP 145
Bergol'ts VM 23
Berkelhammer J 60
Berkelhammer J 61
Berkowitz R 11
Bhatti RA 7
Biondi A 105
Bishop GA 62
Blalock JE 123
Blattner W 146
Boegman RJ 87
Boguslavskii VM 5
Bonmassar E 58
Boraschi D 116
Bordignon C 105
Bostick-Bruton 10
Boyer CM 43
Brahmi Z 31
Brass C 130
Braun DP 126
Bray R 31
Brodt P 114
Brooks CG 44
Brunda MJ 113
Burakoff SJ 96
Burger CJ 54
Burlingham WJ 127
Bursuker I 47
Butterick C 31
Cannon GB 18
Carbone G 53
Carvajal RE 48
Catovsky D 146
Chang C 125
Chang KS 19
Chang KS 20
Chang KS 72
Chang KS 80
Chang KS 81
Chang KS 83
Chang R 125
Chang-Xue Z 30
Chartrand SL 13
Chiao JW 128
Cianciolo GJ 67
Circolo A 58
Clark RA 107
Cohen D 77
Cohen DA 78
Colman M 24
Colombani J 120
Colombo MP 53
Colombo N 16
Colot M 34
Csonka Cs 41
Cupissol D 32
Cupissol D 91
Cuttner J 24
Czako T 41
D'Silva HB 74
Danna V 143
Davidson DD 69
Daynes RA 50
Daynes RA 71
De Chatelet LR 107
De Saint Floren 39
DeMaeyer E 144
Den Otter W 108
Devens BH 100
Drakina LV 5
Drath DB 103
Dubey DP 79
Dupuy D'Angeac 120
Eberlein T 28
Edelstein R 39
Eguchi M 148
Ehrke MJ 92
Ehrke MJ 93
Elgert KD 54
Emeson EE 136
Ensign BM 60
Ensign BM 61
Epremian B 22
Eremeev VS 23
Erickson KL 119
Esteve C 32
Fagiolo E 29
Falkenrodt A 145
Fava L 56
Favier C 32
Favier F 32
Favila L 49
Fidler IJ 119
Fisher RI 10
Fishman M 110
Forni G 111
Forni G 56
Fortner JG 138
Fox M 38
Fukawa M 85
Furukawa T 148
Fuyama S 84
Gajl-Peczalska 13
Gallily R 107
Gallimore PH 42
Gallo RC 146
Gangemi JD 88
Gergely M 41
Giovarelli M 111
Giovarelli M 56
Goldman R 47
Goldstein AL 91
Gomard E 72
Gonzalez R 48
Gordon MY 109
Gordon-Smith EC 109
Gorelik E 113
Gorodilova VV 5
Goto M 14
Gotoda E 83
Green B 33
Green I 77
Griffiths CT 11
Grimm EA 28
Grimm EA 66
Grimm EA 73
Grinevich IuA 95
Gualde N 96
Guinan PD 7
Gupta RK 73
Gurish MF 71
Gutterman GU 35
Gutterman JU 64
Hacker NF 11
Hamilton TA 110
Hammerstrom J 118
Hamuro J 80
Han T 130
Hanatani Y 81
Handa H 3
Hannon MA 100
Harris JE 126
Hashimoto Y 72
Hashimoto Y 83
Hashimoto Y 84
Hassner A 68
Hayami T 80
Heacock EH 76
Hecker CJ 60
Hecker CJ 61
Henney CS 44
Herberman RB 113
Herberman RB 17
Herberman RB 18
Herberman RB 19

Herberman RB 20
Herberman RB 37
Herberman RB 72
Herberman RB 80
Herberman RB 82
Herberman RB 83
Herberman RB 84
Hersh EM 35
Hersh EM 64
Higby DJ 130
Holden HT 113
Holland JF 24
Hollander VP 149
Honma Y 147
Hook RR 60
Hook RR 61
Horiuchi Y 14
Hosokawa M 19
Hosokawa M 81
Hosokawa M 82
Howell SB 89
Howes EL 49
Hozumi M 147
Hu C 125
Hu JN 59
Hubbard A 31
Hui A 65
Huseby RA 51
Introna M 105
Introna M 16
Irimajiri N 121
Ishibiki K 81
Ishida N 37
Ishida N 80
Ishida N 82
Ishida N 83
Ishitani K 37
Israel L 39
Iwama Y 148
Izawa M 80
Izumi T 20
Janiak M 101
Japal KM 90
Johnson HM 123
Johnson WJ 106
Jones KJ 117
Judd MA 117
Kadagidze ZG 5
Kado J 147
Kahan BD 103
Kalyanaraman VS 146
Kamenets LIa 95
Kamiya H 12
Kaplan AM 78
Kashima S 80
Kato K 148
Kawase I 44
Kirchner H 122
Klein E 26
Knapp RC 11
Knop J 144
Knopf B 2
Koessler A 89
Kohi F 135
Kolb R 137
Kolosza Z 9
Kontiainen S 129
Korec S 18
Kottra CJ 36
Koziner B 22
Krammer PH 122
Kreider JW 43
Kubota T 81
Kumagi K 80
Kumai K 81
Kumar V 133
Kuwata T 14
Kwong CH 97
Lacher M 22
LagasseLD 11
Lai M 63
Laing CA 90
Laing LP 87
Landolfo S 111
Lange B 12
Larsen B 112
Lazarus K 31
LeGrue SJ 150
Leonard EJ 107
Leslie CA 79
Levy JP 72
Levy JP 80
Levy JP 82
Levy JP 83
Lieberman P 22
Lill PH 88
Lindquist RR 98
Lohmann-Matthes 47
Longhi B 32
Lotzova E 35
Lotzova E 64
Luna MA 8
Lynch DH 50
Lynch DH 71
Maca R 140
Mace K 93
Macher E 144
Madden L 115
Maguire H 143
Mannick JA 76
Mantovani A 105
Mantovani A 16
Mar'in ND 5
Marcucci F 122
Marinello M 130
Marino PA 106
Mastrangelo MJ 143
Matheson DS 33
Matsumoto S 81
Mavligit GM 139
May L 65
Mayer S 145
Mazumber A 66
Mazumder A 28
McKay P 65
McPherson TA 33
Meltzer MS 107
Mickshe M 137
Mickshe M 34
Migliorati G 58
Mihich E 92
Mihich E 93
Mitchison NA 49
Mitsugi K 80
Miwa H 82
Miyakoshi H 20
Mizel SB 77
Mizushima W 148
Monden M 138
Mora PT 125
Moriguchi S 102
Moriyama M 82
Mueller GC 97
Mukamel E 4
Mukherjee M 25
Munger WE 98
Nakamura K 86
Neumann C 144
Nikol'skii IS 95
Norin AJ 136
Nunn-Hargrove M 83
O'Toole CM 134
Oaki T 84
Obrist R 11
Ogushi F 102
Okuda S 45
Olkowski ZL 1
Olsen RG 141
Ono H 40
Orita K 82
Ortaldo JR 17
Osipov SG 23
Otsuka S 3
Oxenhandler RW 60
Oxenhandler RW 61
Ozaki A 121
Ozer H 130
Pace R 27
Page RH 51
Papp Z 41
Parker L 11
Parmiani G 53
Patriarca P 107
Payne SV 117
Pestka S 35
Petro TM 46
Petro TM 55
Pfeiffer B 145
Pierce CW 142
Pla M 120
Platica M 149
Preta R 56
Prieur DJ 59
Pross HF 15
Puccetti P 58
Putnam JB 70
Quesada JR 35
Raska K 42
Ratnofsky S 96
Reme T 120
Rey A 32
Robert-Guroff M 146
Roberts LK 50
Robinson MK 52
Roder JC 87
Ronald V 55
Rosenberg SA 28
Rosenberg SA 66
Rosse C 124
Rossi F 107
Roth JA 69
Roth JA 70
Roth JA 73

Rucheton M 32
Ruco L 105
Ruco LP 107
Rumiantsev AG 23
Rytwinski K 9
Saffold PC 126
Sahasrabuddhe M 25
Saijo N 121
Sajjad SM 8
Samak R 39
Sarngadharan MG 146
Savary CA 35
Savary CA 64
Saxena QB 57
Saxon A 68
Sazena RK 57
Schade U 47
Schlafli E 93
Schlager SI 115
Schmidt JA 77
Schnaper HW 142
Schneiberg K 9
Schneiderman M 52
Schroit AJ 119
Schwartz SA 62
Segal S 114
Seiji K 84
Selman M 48
Sendo F 20
Sendo F 83
Sendo F 84
Sensi M 53
Serrate SA 17
Serrou B 32
Serrou B 91
Servadio C 4
Sharma BS 94
Shibuya M 121
Shimizu E 102
Shimizu E 121
Shimizu Y 3
Shohat B 4
Silver BA 10
Silver R 24
Skeen MJ 1
Sliski A 146
Smith GD 60
Smith GD 61
Smith JA 38
Smith LA 78
Snoek M 108
Snyderman R 67
Sone S 102
Sordillo PP 22
Starkey JR 59
Starr S 12
Staruch AJ 138
Stebbing N 65
Steinmuller D 127
Stevens A 134
Stevenson HC 119
Stiff MI 141
Stremmer R 144
Strzadala L 92
Suda K 3
Sugarbaker PA 69
Sugita K 148
Sulica A 18
Svedersky LP 65
Szelc S 9
Szmigielski S 101
Tabenska J 9
Taetle R 89
Takenaga K 147
Takeuchi S 19
Takizawa T 121
Talluri K 7
Tan YH 33
Tanimoto K 14
Taylor SG 126
Taylor WA 49
Tedesco 105
Tedesco 116
Terpenning M 75
Tilles JG 94
Tilney NL 76
Timonen TT 17
Tiptaft RC 134
Tomisawa S 107
Tongio MM 145
Trakhtenberg AK 5
Trapeznikov NN 5
Tsubura E 102
Tsubura E 80
Tsubura E 83
Tsukagoshi S 82
Tyan ML 132
Tyler JD 127
Uchida A 137
Uchida A 34
Ullrich S 6
Umanskii VIu 95
Umezawa H 151
Umino T 148
Urdal DL 44
Urushizaki I 19
Urushizaki I 37
Urushizaki I 80
Urushizaki I 81
Urushizaki I 82
Usuda Y 20
Van Loveren H 108
Vanky F 26
Vargas-A F 48
Veith FJ 136
Vose BM 17
Waller M 122
Wanebo HJ 27
Wang BS 76
Warnke RA 21
Watabe S 84
Waters H 131
Watson R 55
Watson RR 46
Watzig F 2
Weinberger O 96
Weintraub J 21
Wheelock EF 52
Whitaker AJ 38
Whitmore AC 111
Wibier-Franqui 72
Wiltrout RH 113
Winkelstein A 99
Wise CC 38
Wong WL 139
Wright DH 117
Yamada Y 81
Yamamoto JK 123
Yamashita J 3
Yoshida T 74
Yoshikai Y 104
Young RC 10
Yumitori K 3
Zheng CX 76
Zighelboim J 75
Zolla-Pazner S 6

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In this issue:

- EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS 1-40
- EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS 41-49
- EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION 50-71
- THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE 72-86
- ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY 87-88
- RELATED BIOLOGY OF IMMUNE CELLS 89-107
- CMI METHODOLOGY 108-113
- SUPPRESSOR CELL ACTIVITY 114-117
- OTHER RELATED STUDIES 118-122

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. IMMUNE DYSFUNCTION FOLLOWED BY IMMUNOSUPPRESSION AFTER CO60 THERAPY IN PATIENTS WITH MALIGNANT TUMOURS.

Kapoor AK, Tiwari MC, Khan IU, Tandon VK, Tuteja N, Siddiqui JS, Mehrotra RM
Postgraduate Dept. Pathology and Bacteriology and Dept., Radiology K.G. Medical Coll., Lucknow, India
J Indian Med Assoc; 77(3/4):45-48 1981

Twenty-one patients of various morphological type were treated by Co60 teletherapy. During pretherapy period higher mean values of absolute lymphocyte counts (ALC), increased levels of lymphocyte sub-populations (active E, total E, IgFc and murine erythrocyte rosette-forming-cell counts) and elevated levels of serum IgG and IgA were detected in patients. Suppression in values of immunological parameters was observed after CO60 therapy. Initial fall was accompanied with recovery in several parameters. Immunological findings during pretherapy period suggested a defect in immune function. Post-therapy responses initially showed generalized immunosuppres-

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sion followed by recovery during 5 wk follow-up period. (Author abstract) (15 Refs)

2. THE OCCURRENCE OF CANCER IN IMMUNE DEFICIENCIES.

Penn I
Dept. Surgery, Univ. Colorado Health Sciences Center, Denver, CO
Curr Probl Cancer 6(10): 64 pp., 1982.

The association of immune deficiency states with increased cancer risk is discussed in detail. Topics covered include components of the immune system (specific immune responses, B cells, T lymphocytes, delayed hypersensitivity cells, cytotoxic T cells, helper T cells, and suppressor T cells), immune amplification mechanisms, nonspecific responses (humoral response, cellular response), immune responses to cancer (reactions deleterious to tumor growth, reactions favoring tumor growth [blocking factors, fetal antigens, alpha2-globulins, small mol wt immunosuppressive factors, suppressor cells, lack of complement]). Also discussed are mechanisms by which tumors escape immune destruction by the host, cancer in immunodeficient states, naturally occurring immunodeficient states, changes associated with organ transplantation (immunosuppressive therapy, transplanted malignancies, cancers arising de novo after organ transplantation [incidence, age and sex of patients, time of appearance of cancers, previous tumors in recipients, malignancies in the donors, types of malignancy]), multiple cancers, treatment, prognosis, effects of immunosuppression on preexisting neoplasms, cancer in uremic patients, second neoplasms arising in patients after cancer chemotherapy and radiotherapy, etiology of neoplasms in immunodeficient states, spontaneous regression of lymphomas, interferons, oncogenic viruses, oncogenic and co-oncogenic effects of immunosuppressive and cancer chemotherapeutic agents, and other potentially oncogenic treatments. (265 Refs)

3. IMMUNOLOGICAL MECHANISMS OF GRAFT-VERSUS-HOST DISEASE IN MAN.

Tsoi MS
Transplantation Biology and Clinical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Transplantation; 33(5):459-464 1982

Immunological studies in clinical graft-versus-host disease (GVHD) and associated phenomena, such as autoimmunity, immunodeficiency, and immune dysfunction are reviewed. Despite the restriction of donor-recipient pairs to human leukocyte antigen-identical siblings and the use of postgrafting methotrexate or cyclosporin A, acute GVHD occur in 30-50% of patients with successful allogeneic bone marrow transplantation (BMT). In 5-10% of all cases, GVHD is associated with fatal complications. Chronic GVHD affects 25-30% of patients surviving for greater than 180 days after transplantation. Humoral immunity is thought to be less important than cellular immunity in GVHD. Articles on the relationship of humoral immunity to GVHD are reviewed. Peripheral T cell profiles in marrow-grafted patients indicate that abnormalities of T cell maturation and imbalance of T cell subset development are not related to GVHD but rather to conditions prevalent after BMT. Lymphocyte proliferative responses in GVHD patients are described. Nonspecific cytotoxicity has been observed in GVHD. The roles of cytotoxic, natural killer, and suppressor T lymphocytes in GVHD are considered. Immunodeficiency is common in patients following BMT. Later, patients without GVHD recover their immune function, while those with chronic GVHD remain immunologically impaired. Aberrations of immune regulation are associated with chronic GVHD. (66 Refs)

4. IMPAIRED IMMUNOCOMPETENCE IN PATIENTS WITH MALIGNANT GLIOMAS: THE POSSIBLE ROLE OF TG-LYMPHOCYTE SUBPOPULATIONS.

Gerosa MA, Olivi A, Rosenblum ML, Semenzato GP, Pezzutto A, Mahaley MS, Salcman M
Instituto di Neurochirurgia, Universita di Padova, Padua, Italy
Neurosurgery; 10(5):571-573 1982

T suppressor (Tg) and T helper (Tm) cells were analyzed in peripheral blood from 10 patients with malignant astrocytoma and 6 with glioblastoma multiforme (7 men, 9 women; 18-71 yr old) as measures of immunocompetence. Tg and Tm cells were detected using IgG- or IgM-coated ox RBC, respectively. Mean percentage of Tm lymphocytes was considered normal both pre- and postoperatively. However, Tg cells were significantly increased preoperatively as compared to 16 normal controls (18.55 +-1.11 vs 12.72 +-1.19, p less than 0.001), and a slight increase was observed after surgery and radiation therapy. There were no significant differences between the two types of gliomas. The postoperative reduction may be related to chemical- or radiation-induced immunosuppression. The increased numbers of Tg cells found in these patients may correlate with the previously reported impairment of immunocompetence in these brain tumor patients. (17 Refs)

5. CELL-MEDIATED IMMUNITY IN CANCER PATIENTS WITH SPECIAL REFERENCE TO LUNG CANCER (II).

Kusumoto S
Dept. Radiology, Yamaguchi Univ. Sch. Medicine, Ube, Yamaguchi Prefecture 755, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(8):792-803 1981

The cell-mediated immunity in 46 patients with lung cancer were evaluated by the technique of in vitro lymphocyte response to phytohemagglutinin (PHA). The relationships between cell-mediated immunity and the clinical stage, prognosis and results of laboratory examinations of the patients were studied. The following results were obtained. (1) The lymphocyte response to PHA in lung cancer patients was significantly lower than that of healthy volunteers. (2) The degree of low lymphocyte response to PHA in lung cancer patients was correlated to the severity of the clinical stage. Especially in the patients with Stage IV the significant difference could be observed statistically. (3) In reference to TNM classification, there were no relationships between the lymphocyte response to PHA and T and N factor. However, significant decrease was found in M1 group compared with M0 group. (4) Lymphocyte response to PHA decreased in the group with poor prognosis and significantly decreased in the group with less than 2 mo of life span compared with the group more than 12 mo. (5) Concerning tuberculin reaction, the negative patients showed significant decrease of the lymphocyte response to PHA. (6) The lymphocyte response to PHA decreased significantly in the patients who had decreased lymphocyte counts or decreased serum protein. (Author abstract) (52 Refs) (In JPN)

6. DEVELOPMENT OF CYTOTOXIC CELLS DURING IN VITRO CULTURES OF PLEURAL EFFUSION LYMPHOCYTES FROM PATIENTS WITH LUNG CANCER.

Uchida A, Micksche M
Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Vienna, Austria
Oncology; 39(4):201-204 1982

Culture-induced cytotoxic (CIC) activity developed in 7-day culture in the presence of fetal calf serum of pleural effusion lymphocytes from patients with lung cancer which initially showed markedly low or no natural killing (NK) activity against K562 cells. The development of CIC activity was proliferation-dependent. The CIC-mediating effector cells were removed by nylon-wool adherence, whereas the NK cells were enriched. Precursors for cytotoxic cells were not clarified. These results suggest that the precursors for cytotoxic cells are present in carcinomatous pleural effusions and able to develop cytotoxicity after 7-day culture in vitro. (Author abstract) (16 Refs)

7. IMMUNOLOGICAL MONITORING OF PATIENTS WITH LARYNGEAL CARCINOMA. CRITICAL CONSIDERATIONS ON THE CURRENT POSSIBILITY OF CLINICAL APPLICATION.

Menzio P, Cortesina G, Sartoris A, Bussi M, Morra B, Cavallo GP, Beatrice F, Di Fortunato V, Poggio E
II Clinica Otorinolaringologica, Universita di Torino, Turin, Italy
Minerva Med; 73(18):1251-1254 1982

The leukocyte migration inhibition factor (LMIF) production by lymphocytes of patients with laryngeal carcinoma after stimulation with 3M KCl extracts from laryngeal carcinoma and laryngeal mucosa was studied as a technique for immunological monitoring of patients with laryngeal cancer. After stimulation with tumor extracts the tests was found to be positive in 65% of all cases and after stimulation with extracts from normal laryngeal mucosa in 8% of all cases in the autologous system. With normal lymphocytes, the test was positive in 90% of all cases with tumor extracts and in 89% of all cases with extract from normal mucosa. With lymphocytes from patients with heterologous laryngeal carcinoma, the test was positive in 90% of all cases with mucosal extract and in 91% of all cases with tumor extract. The high percentage of positive tests in the heterologous system is assumed to be due to differences in the major histocompatibility system. After stimulation with 3M KCl extracts from normal heterologous lymphocytes, LMIF production by lymphocytes from 20 normal subjects was observed in 82% of all cases. (10 Refs) (In ITA)

8. ULTRASTRUCTURE AND MORPHOMETRIC ANALYSIS OF HYPERTROPHIC NUCLEOLI IN NON-HODGKIN'S LYMPHOMA AND PHYTOHEMAGGLUTININ-STIMULATED LYMPHOCYTES.

Shapiro SH, Chang LY, Wessely Z, Klavins JV
Dept. Pathology, Queens Hosp. Center, 82-68 164th St., Jamaica, NY, 11432
Oncology; 39(4):234-241 1982

The ultrastructure of hypertrophic nucleoli in large cells from each of five successive cases of non-Hodgkin's lymphoma (regardless of predominant cell type) showed irregularly rounded or ovoid, mostly compact forms with few scattered light spaces. Occasional nucleolonemal forms were noted. Few ring forms or transitional forms between ring and compact or nucleolonemal types were present. Granular components occupied 78.5 +-1.0% of the mean total area of 132 lymphoma large cell nucleoli of all configurations studied. Hypertrophic nucleoli in 27 phytohemagglutinin (PHA)-stimulated lymphocytes were predominantly nucleolonemal with 74.2 +-10.6% granular composition. The qualitative and quantitative distribution of nucleolar granular moieties did not vary significantly between individual cases of lymphoma nor quantitatively between these and nucleoli in PHA-stimulated lymphocytes. These observations lend further credence to the suggestion of the lymphocyte as a common progenitor cell type for the large B and T cell of malignant lymphomas. Some functional similarity of their nucleoli and those of PHA-stimulated lymphocytes in their participation in ribonucleic acid synthesis is implied. Generally compact nucleoli of lymphomas in contrast to nucleolonemal forms of PHA-stimulated lymphocytes may be pathognomonic for large lymphocytic cells undergoing neoplasia. (Author abstract) (37 Refs)

9. ANGIOIMMUNOBLASTIC LYMPHADENOPATHY: DIFFERENTIAL DIAGNOSIS OF HODGKIN'S DISEASE.

Piguet H
Service d'hematologie, Centre Henri-Becquerel, 76038 Rouen Cedex, France
Gaz Med Fr; 89(14):1609-1610 1982

The physiopathology, development, and treatment of angioimmunoblastic lymphadenopathy (AIL) are described. AIL, characterized by proliferation of angioimmunoblastic cells and of deposits of amorphous, PAS-positive substances, occurs most often during the sixth decade. AIL is often associated with joint and skin disorders and is frequently preceded by allergies or chronic infections. A deficiency of T lymphocytes, particularly T suppressor cells, is observed in AIL along with polyclonal proliferation of B lymphocytes. Corticotherapy and chemotherapy are commonly used to treat AIL. (6 Refs) (In FRE)

10. PHYTOHEMAGGLUTININ OR POKEWEED MITOGEN INDUCTION OF IN VITRO COLONY FORMATION BY T-CELLS FROM PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

Pistoia V, Nocera A, Ghio R, Minale P, Ferrarini M
Dept. Immunology, Univ. Genoa, Viale Benedetto XV, 10, 16132 Genoa, Italy
JNCI; 68(2):233-237 1982

The colony-forming capacity of peripheral blood T-cells isolated from B-cell chronic lymphocytic leukemia patients was studied and compared with that of peripheral blood T-cells isolated from two groups of normal controls (young and aged healthy donors). Upon stimulation with phytohemagglutinin or pokeweed mitogen, T-cells from both the patients and the controls developed into colonies but only in the presence of the appropriate conditioned media. When the responses of the three groups were compared, no statistically significant differences were detected. However, the number of patients who failed to respond to phytohemagglutinin was larger than that of normal controls. Studies on a selected group of patients demonstrated that such unresponsiveness was unrelated to the presence of suppressor cells or to inadequate conditions used for stimulation in culture. Rather, this unresponsiveness may be connected with an intrinsic T-cell defect present in certain B-cell chronic lymphocytic leukemia patients. (Author abstract) (33 Refs)

11. INFECTIOUS MONONUCLEOSIS AND ACUTE LEUKEMIA IN CHILDREN.

Sroczynska M, Sonta-Jakimczyk D, Wojcik Z
Klinika Pediatrii, Instytut Pediatrii S1. AM, ul. 3 Maja 13/15, 41-800 Zabrze, Poland
Pediatr Pol; 56(11/12):1373-1376 1981

Leukemic reaction was seen in a 13-mo-old girl with infectious mononucleosis (IM). She was in good condition 4 mo after treatment for IM. Acute lymphoblastic leukemia with T-lymphocyte receptors was diagnosed in a 2-yr-old girl and a

3.5-yr-old boy with IM. Both patients achieved remissions after intensive polychemotherapy, but died of recurrence. (9 Refs) (In POL)

12. PRELIMINARY IMMUNOLOGICAL EVALUATION OF CARCINOMA OF THE BREAST AND THYROID GLAND.

Abeatici S, Mussa A, Levis P, Sandrucci S, Storta P
Istituto di Clinica Chirurgica II, Universita di Torino, Turin, Italy
Minerva Med; 73(18):1149-1154 1982

Immunological parameters were studied preoperatively and postoperatively in 15 women with malignant tumors (7 with thyroid lesions of the thyroid or of the breast). The total percentage of leukocytes and E rosettes showed a significant difference between the cancer patients and controls and was not affected by surgery. The percentage of B lymphocytes was higher in the cancer patients (2-70%, av 16.4%) than in the controls (4-20%, av 8.1%). The corresponding percentages after surgery were 12.8% and 6%, respectively. The cortisol levels were 100-400 nanog (ng)/ml for cancer patients and 100-250 ng/ml for controls. The mean values were 217.6 ng/ml for cancer patients vs 157.5 ng/ml for controls. The carcinoembryonic antigen (CEA) levels measured before surgery were significantly higher for the patients with thyroid carcinoma than for the patients with goiter. Significant reduction of CEA level was seen after surgery in the cancer patients compared with the preoperative levels. CEA levels were lower in the patients with breast cancer than in those with thyroid carcinoma, and did not differ to much from those measured in the patients with benign breast lesions. CEA levels of the breast cancer patients decreased to 2-3 ng/ml after a slight transient rise shortly after surgery. The IgA, IgG and IgM levels in the patients with thyroid carcinoma were higher than in the patients with benign thyroid lesions. Surgery caused no significant changes in the immunoglobulin levels. (22 Refs) (In ITA)

13. EFFECT OF PERORALLY ADMINISTERED BCG ON RECURRENT BREAST CANCER.

Kimura M
Dept. Surgery, Gunma Cancer Center, 617-1, Takahayashi, Ota, Gunma, Japan
J Surg Oncol; 20(1):65-69 1982

Twenty-eight patients with recurrent breast carcinoma were examined. Of them, 19 were evaluable for an oral route of BCG administration. Seven (37%) have had partial response (6 bone; 1 supraclavicular lymphonodus), 8 (42%) have shown no change, and 4 (21%) have shown failure. No remarkable side effects were observed by this administration. With regard to immunoresponse by oral administration of BCG, all tendencies such as increase of skin reactions, T-cells percent, PHA response of lymphocytes, and decrease of IgG FcR+ T-cells useful for estimating a good prognosis. These data suggest that peroral route of BCG may produce some beneficial effects for bone metastatic lesions of recurrent breast cancer. (Author abstract) (19 Refs)

14. BONE MARROW TRANSPLANTATION.

Hattori K
Third Dept. Internal Medicine, Kanazawa Univ. Sch. Medicine, Kanazawa, Japan
Nippon Rinsho; 39(8):2844-2849 1981

Bone marrow transplantation (BMT) has been performed in more than 2,000 patients all over the world, and more than 50% of the patients had acute leukemia. The rate of success has also been raised from 14%, 4 years ago, to 50-60%, recently. Identical twins are the ideal donors, but donors are usually selected from HLA matched siblings. The patients should be induced to a complete remission before transplantation. Post operative treatments are divided into prevention of graft versus host reaction (GVHR), and the supportive therapy. For prevention of GVHR, methotrexate is most commonly used. Other agents, such as antithymocyte serum which specifically suppresses T lymphocytes, prednisolone, and azathioprine are also often used. Leukemia affects the host's immune system, and the use of the above immuno-suppression agents will further reduce the host's resistance to foreign invasion, patients must therefore be placed in a germ-free room with administration of antibiotics and germ-free food to prevent infection. Despite some social difficulties in Japan, a BMT study group has carried out BMT on nine patients (6 males, 3 females, 18-42 yr old). BMT was used in (2) acute lymphocytic leukemia (ALL), acute premyelocytic leukemia (2), acute myelomonocytic leukemia (1), acute conversion of chronic myelocytic leukemia (1), and in three malignant lymphosarcoma. One 27-yr-old male who had ALL is still alive and well, maintaining a complete remission without chemotherapy. (11 Refs) (In JPN)

15. IN SITU IDENTIFICATION AND ENUMERATION OF HELPER T LYMPHOCYTES IN CUTANEOUS MALIGNANT LYMPHOMAS BY DIPEPTIDYL-PEPTIDASE IV (DPP IV).

Sterry W, Steigleder GK, Goos M, Meisternst E
Dept. Dermatology, Univ. Cologne, Cologne, W. Germany
J Cutan Pathol; 9(2):119-120 1982

Demonstration of dipeptidyl-peptidase IV (DPP IV) was used to reproducibly identify helper T lymphocytes in cutaneous malignant lymphoma. In the plaque stage of mycosis fungoides, the majority of lymphocytes showed DPP IV activity. Thus, mycosis fungoides can be regarded as a malignant helper T lymphocyte proliferation. In the tumor state of mycosis fungoides, DPP IV disappeared from most infiltrating lymphocytes. The decrease of DPP IV-positive lymphocytes may correlate with the onset of the tumor stage and may be of prognostic value. (6 Refs)

16. AUTOLOGOUS LYMPHOCYTOTOXICITY AGAINST SQUAMOUS CELL CARCINOMA IN HEAD AND NECK: II. EVIDENCE OF AUTOLOGOUS LYMPHOCYTOTOXICITY AGAINST TUMOR CELL.

Ikawa T
Dept. Otorhinolaryngology, Kumamoto Univ. Sch. Medicine, 1-1-1 Honso, Kumamoto 860, Japan
Nippon Jibiinkoka Gakkai Kaiho; 84(12):1579-1587 1981

The established cell line, KOIMC-011 (at 18-24 passages) derived from human squamous cell carcinoma, was treated with mitomycin C (MMC) to be used as a cell stimulator. When such MMC-treated KOIMC-011 cells were mixed and incubated with autologous lymphocytes, derived from the host of KOIMC-011, at a lymphocyte/tumor cell ratio of 10:1, lymphocytotoxicity was significantly induced (20.8% 51Cr release) compared to the lymphocytes incubated alone (9.1% 51Cr release). The cytotoxicity was in the T cell fraction and not in the non-T cell fraction, and was blocked by monoclonal anti-human less-2A antibodies. Non-target K562 cells heat treated, rabbit anti-IgG treatment, and phytohemagglutinin treatment did not block the T cell cytotoxicity. When stimulated T lymphocytes were treated with anti-HLA sera, only anti-HLA against CW3 reduced the T cell cytotoxicity. The ability to induce cytotoxicity was not affected by freezing and thawing the tumor cells. These results suggest the possibilities of the involvement of autologous HLA antigen in the destruction of tumor cells, and of specific immunotherapy against human cancers. (32 Refs) (In JPN)

17. IMPAIRED B-CELL DIFFERENTIATION AND T-CELL REGULATORY FUNCTION IN FOUR PATIENTS WITH BLOOM'S SYNDROME.

Taniguchi N, Mukai M, Nagaoki T, Miyawaki T, Moriya N, Takahashi H, Kondo N
Dept. Pediatrics, Sch. Medicine, Kanazawa Univ., Kanazawa, Japan
Clin Immunol Immunopathol; 22(2):247-258 1982

Immunoglobulin-producing ability of lymphocytes from four patients with Bloom's syndrome was evaluated in the in vitro pokeweed mitogen (PWM)- and Nocardia water-soluble mitogen (NWSM)-driven culture systems. Serum levels of three major classes of immunoglobulins, IgG, IgM, and IgA, in patients were decreased as compared with age-matched controls, and the in vitro generation of immunoglobulin-producing cells (Ig-PC) was also impaired in all four patients, to an extent comparable with infant controls. Cellular defects participating in impaired generation of Ig-PC in one patient were assessed in the in vitro cross-over coculture system with autologous and allogeneic combinations of B and T cells and stimulation by PWM and NWSM. These experiments suggested that B-cell differentiation ability and T-cell regulatory function for the generation of Ig-PC were incompletely developed in these patients, as if functional maturation of the patients' lymphocytes had been arrested at the early developmental stages of immune ontogeny. (Author abstract) (30 Refs)

18. B-CELL NEOPLASMS WITH HOMOGENEOUS COLD-REACTING ANTIBODIES (COLD AGGLUTININS).

Crisp D, Pruzanski W
(c/o Pruzanski), Wellesley Hosp., 160 Wellesley St. East, Toronto, Ontario M4Y 1J3, Canada
Am J Med; 72(6):915-922 1982

Among 78 patients with persistent cold agglutinins, 31 had lymphoma, 13 had macroglobulinemia of Waldenstrom, six had chronic lymphocytic leukemia and 28 had chronic cold agglutinin disease. The average age was over 60 yr. Patients with chronic cold agglutinin disease had more hemolytic crises, bleeding and Raynaud's phenomena, and less frequently lymphadenopathy or hepatosplenomegaly. The frequency of anemia, positive Coombs test results, cryoglobulinemia and Bence Jones proteinuria was similar in the various groups. Survival time from diagnosis was on av 2 yr in lymphoma, 2.5 yr in Waldenstrom's macroglobulinemia, more than 6 yr in chronic lymphocytic leukemia and more than 5 yr in chronic cold agglutinin disease. Anti-I were common in chronic cold agglutinin disease and rare in other groups. Anti-I and other cold agglutinins were rare in chronic cold agglutinin disease and common in lymphoma and Waldenstrom's macroglobulinemia. In chronic cold agglutinin disease, and in Waldenstrom's macroglobulinemia, cold agglutinins usually had kappa light chains -92% and 71%, respectively - whereas in lymphoma, 71% of cold agglutinins had lambda light chains. The type of light chains related to the specificity of cold agglutinins. Cold agglutinins were cytotoxic to autologous and allogeneic lymphocytes. Occasionally, more autologous than allogeneic cells were killed implying that the former may be precoated in vivo with the antibodies. In conclusion, conditions with persistent cold agglutinins are a spectrum that varies from 'benign' autoimmune-like chronic cold agglutinin disease to malignant lymphoma. Marked differences in the light chain type of cold agglutinins, specificity toward membranous antigens and severity of clinical manifestations were noted in benign and malignant varieties. (49 Refs)

19. REACTIVITY OF HUMAN LYMPHOCYTES TO TERATOMA PREPARATIONS AS REVEALED BY THE MACROPHAGE ELECTROPHORETIC MOBILITY (MEM) TECHNIQUE.

Irmscher J, Grossmann H, Kotzsch M, Wagner H, Muller M
Institut fur Pathologie, Medizinische Akademie 'Carl Gustav Carus' Dresden, Fetscherstr. 74, DDR-8019 Dresden, E. Germany
Arch Geschwulstforsch; 52(5):349-353 1982

Reactivity of lymphocytes from cancer patients to extracts of teratoma tissues was studied by means of the macrophage electrophoretic mobility (MEM) test. Metastastic tissue of a malignant mediastinal teratoma in a young man and tissue of a malignant abdominal teratoma in a girl were used. Both teratomas contained elements of all three germ layers. Extracts were made using 3 M KCl. Lymphocytes were obtained from 119 patients with various types of cancers, 46 healthy controls, and 47 patients with benign diseases. Samples of 10(6) lymphocytes were incubated with 200 ul of extract for 90 min at 297 K. MEM tests were conducted using guinea pig peritoneal macrophages mixed with supernatants from the lymphocytes to be tested. Reduction of MEM by the supernatant was considered a positive reaction to lymphokines released by the lymphocytes. Positive reactions were obtained with lymphocytes from 19 cancer patients and 15/93 controls and noncancer patients. Positive, results were obtained from 41/47 patients with colorectal cancer, 23/26 with gastric or esophageal cancer, 23/25 with otorhinolaryngological carcinoma, 5/7 with breast cancer, 11/12 with other cancers, and 2/2 with teratoma. Positive results were obtained from only 1/46 healthy controls but 14/47 patients without malignancies. Sensitivity to certain antigenic properties of teratomas evidently occurs in patients with cancers and also in patients with certain benign conditions. Whether this sensitivity is due to one antigen or to more than one is uncertain. (8 Refs)

20. THE CORRELATION OF ADENOSINE DEAMINASE AND PURINE NUCLEOSIDE PHOSPHORYLASE ACTIVITIES IN HUMAN LYMPHOCYTES SUBPOPULATIONS AND IN VARIOUS LYMPHOID MALIGNANCIES.

Demeocq F, Viallard JL, Boumsell L, Richard Y, Chassagne J, Plagne R, Lemerle J, Bernard A
Centre Jean Perrin, B. P. 392, 63011 Clermont-Ferrand Cedex, France
Leuk Res; 6(2):211-220 1982

Activities of adenosine deaminase (ADA) and purine nucleotide phosphorylase (PNP) were measured in normal human T cells and in the tumor cell populations from 62 children and 27 adults with lymphoid malignancies. Thymocytes had high ADA activity and low PNP activity, whereas T-peripheral blood lymphocytes (PBL) had low ADA activity and high PNP activity. Malignant B-cell populations had low values of ADA activities and intermediate values of PNP activities similar to E rosette formation negative PBL. Non-T, non-B acute lymphocytic leukemia (ALL) patients had cells with high values of ADA activities and moderate values of PNP activities. A linear correlation between ADA and PNP activities was observed in cells from non-T, non-B ALL, whereas such a correlation did not appear in cells from T-ALL or T-lymphoblastic lymphomas. HLA-DR negative common ALL cell populations had high values of ADA as compared to HLA-DR positive common ALL cell populations. In contrast with HLA-DR, presence or absence of common ALL antigen, as defined by Mo.Ab J5, did not appear to correlate with the level of the enzyme activities. Particularly no clear distinction between the subgroup of malignancies that could be related to corticothymocytes and the subgroup related to medullary thymocyte in terms of both ADA and PNP activities could be disclosed, and large ranges of values were observed in both subgroups. No correlation appeared to occur in the group of T-cell lymphoid malignancies, whereas a correlation existed in cells from children with non-T, non-B ALL. (37 Refs)

21. SPONTANEOUS CELL MEDIATED CYTOTOXICITY IN PATIENTS WITH TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER. DIFFERENCE IN EFFECTOR CELL POPULATION (MEETING ABSTRACT)

Moroz C, Lindner A, Twaig S, Madgar I, Many M
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Lymphocytes isolated from the blood of transitional cell carcinoma (TCC) like those of control patients were capable of mediating spontaneous cell-mediated cytotoxicity (SLMC) against K-562 cells. When this natural cytotoxicity was analyzed with regard to the effector cell type it was found that in TCC patients the SLMC was mostly displayed by E-rosetting T-lymphocytes whereas, compared to controls, a significant decline in the SLMC of the non-T lymphocytes was observed. The SLMC of the T lymphocytes derived from TCC patients was further demonstrated on a T-leukemia target cell (Peer). When comparing the SLMC on both K-562 and Peer target cells, a specificity difference was observed between TCC and the control patient effector cells. The SLMC activity of the TCC patients T cells was not abolished after depletion of Fc receptor positive cells as well as following treatment with monoclonal antibodies OKT 8 or OKT 4 and complement (C'). (no Refs)

22. CHEMOIMMUNE PROPHYLAXIS OF SUPERFICAL BLADDER CANCER (MEETING ABSTRACT)

Adolphs HD, Bastian HP
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We developed the concept of chemoimmune prophylaxis of bladder cancer on the basis of experimental findings. In January 1978, we introduced this concept of recurrence prophylaxis of superficial bladder cancer as a pilot study into clinical praxis. Fourteen days after complete tumor resection, 700 mg/m2 cyclophosphamide was given intravenously. Two weeks thereafter, we began intravesical BCG instillations using 120 mg strain Connaught BCG/50 normal saline. At the same time BCG skin scarification was performed. This intravesical and percutaneous BCG treatment was repeated 5 times in weekly intervals. We have currently treated more than 80 patients with T1 grade I, II or III transitional cell carcinomas. Our preliminary results reveal a decrease of tumor recurrences in the BCG treated patient group compared with a retrospective group of 65 well controlled untreated cases. Reviewing our results theoretically 3 possible immunological mechanisms have to be considered: 1) Cyclophosphamide inhibits the precursors of suppressor T cells resulting in stimulation of the cytotoxic immune response against the tumor. 2) The humoral immune response is depressed by cyclophosphamide with consequent inhibition of immune complex formation correlating with tumor enhancement. 3) BCG exerts a tumor destructive effect by means of a chronic granulomatous inflammation and a nonspecific stimulation of tumor immunity. (no Refs)

23. DIMINISHED HELPER-T-LYMPHOCYTE FUNCTION IN CANCER PATIENTS.

Umeda T, Hara T, Koseki K, Kobayashi K, Akaza H, Niijima T
Dept. Urology, Faculty Medicine, Univ. Tokyo, Bunkyo-ku, Tokyo, Japan
Cell Mol Biol; 28(1):67-71 1982

The induction of immunoglobulin-secreting cells (IgSC) was studied in peripheral blood lymphocytes (PBL) from patients with malignant tumors of the urogenital tract. PBL were cultured in the presence of pokeweed mitogen (PWM) and the number of IgSC was enumerated by reverse plaque technique. It was shown that the generation of IgSC was impaired in lymphocytes from patients with malignancies as compared with those from normal controls. Then, cellular sites responsible for the reduced generation of IgSC in the cancer patients were determined. B-cells from cancer patients generated almost the same number of IgSC as those from normal controls in PWM-stimulated cultures with allogeneic normal T-cells. T-cells from cancer patients showed reduced capacity to induce IgSC in cooperation with allogeneic normal B-cells, as compared with those from normal controls. The generation of Con A-activated suppressor-T cells was not impaired in PBL from cancer patients. Mitomycin-C-treated normal T-cells enhanced the generation of IgSC by allogeneic normal B-cells and the capacity was not impaired in T-cells from cancer patients. From the results obtained, it was suggested that helper-T cells but not suppressor-T-cells nor B-cells were deteriorated in patients with malignancies of the urogenital tract. (Author abstract) (13 Refs)

24. PSEUDOLYMPHOMA WITH MYCOSIS FUNGOIDES MANIFESTATIONS, HYPERRESPONSIVENESS TO DIPHENYLHYDANTOIN, AND LYMPHOCYTE DISREGULATION.

Rosenthal CJ, Noguera CA, Coppola A, Kapelner SN
Div. Heamtology/Oncology, Downstate Medical Center, Box 20, 450 Clarkson Ave., Brooklyn, NY, 11203
Cancer; 49(11):2305-2314 1982

Three patients receiving diphenylhydantoin (DPH) were seen with a reversible process suggesting mycosis fungoides. Clinical and laboratory manifestations included generalized pruritic exfoliative erythroderma, eosinophilia, lymphadenopathy, hepatosplenomegaly, circulating Sezary cells, epidermal Pautrier's microabscesses on skin biopsy, and moderate liver dysfunction. Studies of the distribution and function of the various lymphocyte subpopulations from these patients showed: (1) an increase in the relative and absolute number of T lymphocytes (85-92%); (2) significant stimulation of lymphocyte-blastic transformation by DPH and low response to pokeweed mitogen stimulation; (3) the impaired ability of Tgamma lymphocytes to suppress B-cell differentiation and immunoglobulin production. With only one exception, 15 symptom-free patients on DPH showed none of these abnormalities. The clinical manifestations and immunologic abnormalities of patients with this pseudo mycosis fungoides syndrome remitted 3-4 wk after DPH administration was discontinued. The proliferation of T lymphocytes and the inhibition of the function of tgamma-suppressor lymphocytes noted in these patients may be significant to the development of other types of pseudolymphoma and to that of true lymphoma. (Author abstract) (24 Refs)

25. PHYTOHEMAGGLUTININ-INHIBITION OF THE LEUCOCYTE MIGRATION IN PATIENTS WITH BREAST CARCINOMA: CORRELATION BETWEEN CLINICAL STAGE AND IMMUNOCOMPETENCE.

Pacheco-Rupil B, Depiante-Depaoli M, Trevino E, Bengolea O
Laboratorio Central Hosp. Nacional de Clinicas, Santa Rosa 1564 5000 Corboda, Argentina
Cell Mol Biol; 28(1):73-77 1982

Cell-mediated immunity (CMI) was evaluated in 58 patients with breast carcinoma by the inhibition of the leukocyte migration in response to phytohemagglutinin (PHA). The tests were assessed in the presence of autologous and normal AB homologous plasmas. The patients were divided according to Manchester classification into 4 groups: stages I, II, III and IV. The patients in Stages I and II of the disease showed no significant differences with regard to the normal controls when their leukocytes were tested in the presence of homologous plasma. Conversely, there were significant defects in the response of PHA in Stages III and IV when compared to controls and patients in Stages I and II a suppressive effect was observed in all stages when the assays were performed in the presence of autologous plasma. The incidence of this effect increased along with the extension of the disease reaching highly significant values in Stages I and III-IV with regard to the control group. A different behavior was observed in some cases in Stages II and III-IV since the leukocytes seemed to revert their negative response to a positive one, when tested with their own plasma. None of these effects were observed in the control group. We conclude that PHA-leukocyte migration inhibition is a useful test in the evaluation of CMI and regulatory plasmatic factors in patients with breast carcinoma. (Author abstract) (18 Refs)

26. RELATIONSHIP OF PRETREATMENT LYMPHOBLAST PROLIFERATIVE ACTIVITY AND PROGNOSIS IN 97 CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

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Blood; 59(6):1197-1202 1982

We have analyzed the pretreatment 3H-thymidine labeling indices in blood and marrow blast cells from 97 children with acute lymphoblastic leukemia (ALL) and circulating blasts. The median marrow labeling index (LI) was 6.2% (range 0.8%-32.7%) and the median blood LI, 3.2% (range 0.3%-20%). Blood LI was significantly correlated with leukocyte count and rosette-forming (E+) lymphoblasts but not with central nervous system leukemia or thymic mass at diagnosis. Marrow LI was related to E+ blasts only. In children with E+ leukemia, both blood and marrow LIs were significantly higher than values for other ALL subtypes (p less than 0.01) excluding undifferentiated ALL, which was characterized by an increased blood LI. Eighteen patients had a blood LI that either equaled or exceeded the marrow LI; apart from age, the clinical features, blast phenotypes, and treatment responses of this group were similar to those of patients with blood LI less than marrow LI. Among 51 patients assessed for treatment response, the estimated median length of remission was significantly shorter for those with a blood LI greater than 4% ($p = 0.002$) or a marrow LI greater than 6% ($p = 0.011$). By Cox-regression analysis, the pretreatment proliferative activity of blood and marrow blasts, unlike other initial features studied, added significant prognostic information to leukocyte count in these patients with circulating blasts. The findings provide a cogent explanation for the differential clinical responsiveness of commonly recognized ALL subclasses. (Author abstract) (30 Refs)

27. ANGIOIMMUNOBLASTIC LYMPHADENOPATHY WITH HYPOGAMMAGLOBULINEMIA. POSSIBLE ROLE OF MONOCYTE SUPPRESSION.

Rice L, Abramson SL, Laughter AH, Wheeler TM, Twomey JJ
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Am J Med; 72(6):998-1004 1982

A patient with angioimmunoblastic lymphadenopathy had low serum immunoglobulin values and no antibodies to injected immunogens. This occurred despite the proliferation of polyclonal B cells. T cells were deficient in number and in lymphoproliferative responses, but their helper and suppressor functions were maintained. Ia-antigen bearing leukocytes from the patient stimulated poorly in mixed leukocyte culture. In vitro immunoglobulin synthesis by mononuclear leukocytes from the patient were severely impaired. These leukocytes actively suppressed immunoglobulin synthesis by normal cells from healthy subjects in co-culture. The responsible cell had characteristics of a monocyte. The suppression was selective for humoral immunity and was manifest despite normal numbers of monocytes. It appears that heterogeneous immunoregulatory abnormalities can underlie the syndrome of angioimmunoblastic lymphadenopathy. Furthermore, monocyte suppressor abnormalities may be implicated in clinical disease phenomena. (Author abstract) (39 Refs)

28. INFLAMMATORY RESPONSE IN PATIENTS WITH MALIGNANT LYMPHOMAS.

Bambara LM, Corrocher R, Celebrano R, Martinelli L, Chilosi C, De Sandre G
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Haematologica (Pavia); 67(2):207-215 1982

Chemotactic and phagocytic functions of polymorphonuclear neutrophils (PMN) and monocytes were assayed in 11 patients (9 males, 2 females, 18-68 yr old) with Hodgkin's lymphoma (HL) and 11 patients (6 males, 5 females, 46-71 yr old) with non-Hodgkin's lymphoma (NHL) using the skin window test (SWT). Diagnosis was histologically confirmed. All patients were studied at the time of diagnosis and prior to therapy. Results were compared with those obtained from 20 normal volunteers. The main feature of SWT in HL patients was the delayed PMN phase; at 3 hr the mean total number of PMN was 3,880 +-2,510/coverslip, significantly lower than normal. The nadir was observed at 6 hr (7,890 +-5,420/coverslip). The behavior of PMN-phase was rather constant regardless of clinical stage and histological type of disease, except for persistent depression of the number of PMN in one patient. No difference in the morphology of cells compared with the control group was observed using May Grunwald Giemsa staining. In all groups after 12 hr, a few monocytes showed a positivity for leukocyte alkaline phosphatase varying from + to ++. This finding may be the expression of a false positivity due to debris of cells phagocytosed or alternatively represents the transition to macrophages. In patients with either HL or NHL, the positivity for non-specific-esterase (NSE) was more pronounced than in normal controls, even during the first hours of SWT. In 5/10 patients, 40-60% of monocytes were NSE ++ or +++ and 2/10 were NSE

+ + or + + + in approx 20% of monocytes at 3 hr. Thus, chemotaxis and the phagocytic process are severely impaired in NHL, particularly in the late stages. (25 Refs)

29. PHAGOCYTOSIS AND INTRACELLULAR KILLING BY PERIPHERAL BLOOD MONOCYTES OF PATIENTS WITH MONOCYTIC LEUKEMIA.

van Furth R, Leijh PC, Van Zwet TL, Van den Barselaar MT
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Blood; 59(6):1234-1238 1982

This article concerns a study on the endocytic functions of circulating monocytes from 12 patients with acute or chronic monocytic leukemia. The results show that phagocytosis and intracellular killing of Staphylococcus aureus are impaired in only two patients and that the opsonic activity of the serum of all patients is normal. With respect to the intracellular killing of ingested Staphylococcus aureus, an interesting phenomenon was found in that the cells of patients with monocytic leukemia proved to be in a state of activation, as shown by the finding that patients' monocytes with normal phagocytosis killed about 64% of the ingested bacteria in the absence of extracellular stimulation by serum factors. When extracellular serum was present, the mean killing index rose to only 69%. This is unlike the situation seen in monocytes from healthy donors, where no killing occurs in the absence of extracellular serum and extracellular stimulation by serum factors is mandatory for optimal intracellular killing. (Author abstract) (9 Refs)

30. IN VIVO AND IN VITRO IMMUNOLOGICAL MONITORING IN CARCINOMA OF THE UTERINE CERVIX.

Sacco F, Benedetti Panici P, Di Roberto P, Margariti PA, Villani L, Laghi V, Cauda R, Nervo P
Istituto Clinica Ostetrica e Ginec., Univ. Catt. Sacro Cuore, Rome, Italy
Minerva Ginecol; 34(4):259-264 1982

The immune status of 22 patients with carcinoma of the uterine cervix was evaluated by the E rosette test, by determining the circulating immunocomplex levels and by the dinitrochlorobenzene (DNCB) skin test before treatment. Six patients were in Stage I-B, five in II-A, eight in II-B and three in III-A. Eighteen healthy women served as controls. The E rosette and DNCB skin tests demonstrated impaired cell-mediated immunity. The percentages of e rosettes were 37.3% in Stage I-B, 36.6% in II-A, 32.5% in II-B and 29% in III-A vs 54.7% in the controls. The circulating immunocomplex levels were increased significantly in 77% of all patients. The DNCB scores averaged 1.1 +-1.2 in Stage I-B, 1.0 +-1.2 in II-A, 1.0 +-1.06 in II-B and 0.66 +-0.57 in III-A. (49 Refs) (In ITA)

31. CELL-MEDIATED IMMUNITY AND VERRUCOSIS: AN IN VITRO STUDY.

Kokelj F, Presani G, Perticarari S, Trevisan G
Clinica Dermatologica, Universita di Trieste, Trieste, Italy
G Ital Dermatol Venereol; 116(12):527-531 1981

The cell-mediated immunity was studied in 33 patients (14 men and boys and 19 women and girls; 8-69 yr, av age 19 yr) with verrucosis refractory to conventional treatment by evaluating the increase in the percentage of E rosettes in lymphocyte cultures incubated with levamisole in the presence of sheep erythrocytes. None of the patients underwent immunomodulating treatment, nor had diseases caused by immunodeficiency. The percentages of E-rosette-forming lymphocytes were clearly pathological (below 50%) in 8/33 patients, and were normal or slightly below the control values in the other 25. In the presence of levamisole the increase in the percentage of E rosettes was below 10% in 10/33 patients, and the difference from the controls was not significant. The increase exceeded 10% in the 23 other patients: the median increases was 16.05% in 8/23 patients with immunosuppression demonstrated by the E rosette test and 18.295% in 15/23 patients without impairment of cell-mediated immunity. The results of the EAC test, performed in 15/33 patients, were normal, showing no significant difference from the controls. The results suggest that verrucosis refractory to conventional treatment could be the only clinical sign of cellular immunodeficiency. (28 Refs) (In ITA)

32. IMMUNOLOGIC STUDY OF THE CANCER PATIENT.

Morel CJ, Pilheu FR, Tomeo A, Bassi R, Ahumada JC, Pascon G
IV Catedra de Cirugia, Hospital de Clinicas 'Jose de San Martin', Buenos Aires, Argentina
Rev Argent Cir; 42(1/2):73-79 1982

An immunologic study (IS) was carried out on 211 patients with cancer (83, digestive tract; 50 mammary gland; 10, pulmonary; 14, genitourinary; 13, mouth; and 41, at other sites) using tests for delayed skin hypersensitivity (bacteria, fungi, and dinitrochlorobenzene) and for spontaneous rosette formation. The IS was executed before surgery in 71 of the patients, before and after in 34, before and during radiotherapy (RT) in 7, before and during chemotherapy (CT) in 38, during CT in 40, and after surgery in 21. Best results were obtained using candidine and purified protein derivative (PPD) in the hypersensitivity tests. Results of the IS were positive in 46% of the patients before surgery, in 66% after surgery, in 79% of those who had tumor removed, and in 37.5% of those who did not have tumor removed. The RT did not influence appreciably the results of the IS. Of the 83 patients tested before, during, and after the CT, 69 did not show any change, 7 became more positive, and 7 became more negative. Results of the rosette test were positive in 77% of the patients studied before surgery and in 73% studied after. Results of the rosette test agreed with those of the skin tests in 66% of the patients studied before surgery and in 72% studied after. It was suggested that nutritional state plays a major role in the immunologic status and prognosis of patients with cancer. (14 Refs) (In SPA)

33. IMPLICATIONS OF PERSISTENT T CELL ABNORMALITIES FOR THE ETIOLOGY OF HODGKIN'S DISEASE.

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Cancer Treat Rep; 66(4):681-687 1982

Untreated patients with Hodgkin's disease are known to have significant impairment of cellular immunity. Recent studies have demonstrated that effector T cells from these patients have increased sensitivity to the suppression mediated by two normal immunoregulatory cells, ie, suppressor monocytes and suppressor T cells. Thus, increased sensitivity to suppression may be a common cause of multiple abnormalities of cellular immunity. Patients achieving long-term disease-free survival after chemotherapy have also been studied. Although they are no longer anergic, they have persistent reductions in peripheral blood E rosettes and T cell proliferation. Increased sensitivity to suppressor monocytes and T cells also persists. These abnormalities do not appear to be caused by the treatment since they were not detected in diffuse histiocytic lymphoma patients surviving after similar chemotherapy. Immunologic studies in family members are required to determine whether these abnormalities are a permanent immunologic deficit acquired only with the development of Hodgkin's disease or an inherited characteristic that predisposes a patient to develop Hodgkin's disease. (Author abstract) (22 Refs)

34. FUNCTIONAL PROPERTIES OF NATURAL KILLER CELLS IN CARCINOMA OF THE PROSTATE (MEETING ABSTRACT)

Wirth MP, Schmitz-Drager BJ, Ackermann R
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Natural killer (NK) - cells are believed to participate in the immunological defense of malignant tumors. Earlier experiments have shown a reduced spontaneous cell-mediated cytotoxicity (SCMC) in patients with advanced carcinoma of the prostate (CaP). Aim of this study was to investigate reasons for the depressed SCMC in advanced CaP. SCMC was determined in a 51Cr-release assay with peripheral mononuclear cells (PMC) from 5 patients with localized CaP, 8 patients with advanced CaP and 5 healthy male donors. Mononuclear cells from regional tumor-draining lymph nodes of 4 patients with localized CaP and 4 tumorfree patients were examined for their SCMC. Various tumor cell lines originating from CaP and other tumors served as target cells. Functional properties of NK-cells were analyzed by stimulation with human interferon-beta (IFN-beta). The experiments revealed a significant increase of SCMC following IFN-beta stimulation even in patients with advanced CaP indicating the normal function of peripheral NK-cells in these patients. The reduced SCMC in advanced CaP may be explained by a diminished number of mature NK-cell or by inhibitory mechanisms. IFN-beta stimulation did not improve the reactivity of mononuclear cells from tumor-draining lymph nodes of patients with localized CaP, whereas nodal mononuclear cells from tumorfree patients responded to IFN-beta stimulation. This finding is indicative for a disorder of NK-cells in the tumor-draining lymphatic system in patients with CaP. (no Refs)

35. EPSTEIN-BARR VIRUS (EBV)-LYMPHOID CELL INTERACTIONS. II. THE INFLUENCE OF THE EBV REPLICATION CYCLE ON NATURAL KILLING AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY AGAINST EBV-INFECTED CELLS.

Patel PC, Menezes J
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Clin Exp Immunol; 48(3):589-601 1982

We investigated the influence of the Epstein-Barr virus (EBV) replication cycle on natural killing (NK) activity and antibody-dependent cellular cytotoxicity (ADCC) against EBV-infected cells. Peripheral blood lymphocytes from healthy EBV-seropositive and -seronegative donors were separated on Ficoll-Hypaque gradients and used as effector cells in the standard 51Cr release assay to measure NK and ADCC. EBV-genome positive RAJI and DAUDI cells superinfected with either the non-transforming P3HR-1 EBV or the transforming B95-8 EBV were used as targets. The results obtained show that most normal individuals have ADCC and NK activity against P3HR-1 EBV-infected RAJI cells. Both the cytotoxic activities increased with the proportional increase in effector/target (E/T) ratios, assay incubation time, dose of the infecting virus and the time of pre-infection with EBV. Moreover, the data obtained indicate that different immune mechanisms are effective at different stages of the virus replication cycle. During the early stages of virus replication, EBV-superinfected cells are more susceptible to ADCC than to NK, whereas in later stages the susceptibility to NK is increased significantly and appears to play a more dominant role. The nature of the target cells or the strain of EBV used to superinfect these targets did not influence their susceptibility to ADCC and NK activity; however some quantitative differences were found. Using metabolic inhibitors such as cytosine arabinoside, phosphonoacetic acid, actinomycin D, cycloheximide and puromycin, it was found that new DNA synthesis is not essential but some RNA and protein synthesis is necessary, late in the viral cycle, for the superinfected cells to become susceptible to NK and ADCC. (Author abstract) (34 Refs)

36. RETINOIDS ENHANCE CELL-MEDIATED IMMUNITY IN VIVO (MEETING ABSTRACT)

Fulton RA, Souteyrand P, Thivolet J
Department of Dermatology, Royal Infirmary, Glasgow, Scotland
Scott Med J; 27(1):95 1982

Synthetic derivatives of vitamin A (retinoids) have recently been shown to exert a marked therapeutic effect on disorders of keratinization such as psoriasis and ichthyosis as well as in prevention of epithelial neoplasms. Retinoids may act by enhancing cell-mediated immunity which may be depressed in these conditions. A study was carried out to test this hypothesis using the oral retinoid RO 10-9359 in patients with psoriasis and other dermatoses. Twenty-six patients with psoriasis and 123 patients with other dermatoses were tested for 28 days with oral retinoid RO 10-9359. Intradermal tests to 7 recall antigens were carried out before and after therapy. Dinitrochlorobenzene (DNCB) sensitization was commenced at the start of retinoid therapy and challenge tests were made after 20 days. There was a significant increase in reaction to recall antigens in all groups after 28 days' retinoid therapy. The reaction to DNCB was increased only in the non-psoriatic group compared with controls. These results demonstrate that the retinoid RO 10-9359 stimulates cell mediated immunity in vivo. This may explain part of the action of this new group of drugs as well as their role in cancer prevention. (no Refs)

37. CANCER: ACHIEVEMENTS, CHALLENGES, AND PROSPECTS FOR THE 1980S. VOLUME 1.

Burchenal JH, Oettgen HF
Memorial Sloan-Kettering Cancer Center, New York, NY
Cancer: Achievements, Challenges, and Prospects for the 1980s. Volume 1. New York, Grune and Stratton, 685 pp., 1981.

The current status of cancer research and prospects for the future are reviewed. Topics include epidemiology (analytic epidemiology, epidemiology and cancer control policy), viruses (polyoma, feline leukemia, sarcoma, Epstein-Barr viruses, retroviruses), radiation hazards (radiation and thyroid, breast, and childhood cancers), industrial and lifestyle carcinogens (metabolic activation of chemical carcinogens, tumor registries), host defense against cancer (immunogenetics of cancer in man and animals, cell-mediated immune reactions to human cancer antigens and their regulation, biochemistry of human tumor antigens), genetics (genetic epidemiology of human cancer, specific fine structural chromosome defects in human neoplasia, clinical features and management of genetic cancers), cell biology and cancer (evolution of the malignant cell phenotype, properties of metastatic tumor cells), prevention of carcinogenesis (inhibitors of chemical carcinogens, advances in the use of retinoids for cancer prevention, blocking of tumor promotion by protease inhibitors), and advances in diagnosis (biochemical and immunologic diagnosis of cancer, advances in nuclear imaging, early diagnosis of liver cancer, advances in diagnosis of gastrointestinal neoplasms). (1641 Refs)

38. IMMUNOLOGICAL ABNORMALITIES IN ORAL CARCINOMA AND ORAL KERATOSIS.

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J Maxillofac Surg; 10(2):113-115 1982

Examination of serum concentrations of IgG, IgA, IgM, IgE, and IgD in oral carcinoma and oral keratosis confirmed a rise in serum IgA concentration in oral carcinoma and revealed a rise in IgE. In oral carcinoma, other serum immunoglobulins were present in normal concentrations. Serum IgA and IgE were not increased in oral keratosis but IgM was reduced, with normal levels of other immunoglobulins. The results may reflect changes in cell-mediated immunity rather than simply changes in humoral immunity. (Author abstract) (39 Refs)

39. IMMUNOCOMPETENCE AND MALIGNANCY.

Melief CJ, Schwartz RS
Hematology Service, New England Medical Center Hosp., Boston, MA
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Present concepts regarding immunocompetence and malignancy are reviewed. The general applicability of the theory of immunological surveillance to the pathogenesis of cancer is questioned. Immunological surveillance arguments fail to acknowledge the parallel system of adaptive immunity - blocking antibody - which protects the tumor against the cell-mediated immunity of the host. The virulent virus strains that are used to demonstrate immunosuppression by oncogenic viruses are not considered to have any relevance to malignancies as they develop naturally. The issue of defense mechanisms against oncogenic viruses through infectious agents must be separated from that of the defense against the cells they have transformed to a malignant state. In nearly all studies designed to determine the subject's ability to respond to antigens of his own neoplasm, evidence for cell-mediated immunity against antigens of the tumor (either from the patient or from a histologically similar allogenic tumor) has been found. Two experimental models are consistent with the notion that unrestrained proliferative activity of lymphoid tissue can culminate in neoplasia: persistent antigenic stimulation combined with partial immunosuppression and chronic graft vs host reactions. Recent experimental results now permit a serious examination of the notion that the immune reaction stimulates the growth of tumors. (267 Refs)

40. TOPICAL IMMUNOLOGICAL FINDINGS IN CARCINOMA OF THE BLADDER.

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Z Urol Nephrol; 75(3):153-157 1982

The current status of immunology in the diagnosis and treatment of carcinoma of the bladder is reviewed. In general, data are available for only a small number of test subjects. In vivo skin tests of the tuberculin type have been conducted using the recall antigens for tuberculin, candidin, streptokinase, mumps, and trichophytin. In almost all cases a secondary response was obtained. Dinitrochlorobenzene (DNCB) and dinitrofluorobenzene (DNFB) were used as primary antigens. Primary and secondary antigen tests provided an indication of the general state of a patient's immune system. No direct indication of tumor growth was obtained. Skin tests were therefore useful for prognosis but not diagnosis. Tests using extracts of tumor tissue apparently are more informative, but ethical questions make the use of them in normal individuals and cancer patients not advisable. In general a weak response to a skin test indicates poor prognosis. The strength of reactions decreases with advance tumor growth, but this decrease is statistical and cannot be used to evaluate individual cases. In vitro measurement of carcinoembryonic antigen and fibrinogen cleavage products is evidently useful for determining recurrence of tumors but not for diagnosis. Cytotoxicity tests of cell-mediated immunity are apparently reasonable sensitive and specific, but insufficient data has been obtained to allow a definite conclusion. Immunotherapy using BCG applied by various methods has produced improvement in some patients and in some studies in animals bearing experimentally induced tumors. (50 Refs) (In GER)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

41. IDENTIFICATION OF EFFECTOR T CELLS RESPONSIBLE FOR ENHANCED ANTITUMOR IMMUNITY INDUCED BY TUMOR VACCINE AND PYRAN COPOLYMER.

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Cancer Immunol Immunother; 12(3):247-253 1982

Antitumor effector cells were studied in mice primed with Concanavalin A (ConA)-bound L1210 murine leukemia cell vaccine and pyran copolymers (PC). L1210-bearing mice received ip injections of ConA-bound or ConA-free L1210 vaccine and/or PC and were examined for survival. A single inoculation of ConA-bound L1210 vaccine or PC prolonged the life-span of mice marginally but significantly. Mice primed ip with ConA-bound L1210 vaccine and/or PC were inoculated ip with live L1210 cells and examined for survival. A single inoculation of ConA-bound L1210 vaccine or PC did not prolong the life-span of mice that subsequently received injections of live L1210 cells. However, in combination, ConA-bound vaccine and PC, administered successively with a 3-day interval, induced strong antitumor activity. The peritoneal cells of unprimed or L1210 vaccine-primed mice inhibited L1210 cell proliferation marginally, if at all, while those of PC-primed mice effected strong inhibition. Recipient mice inoculated simultaneously with spleen and peritoneal cells from primed mice and 10(2) live L1210 cells did not live any longer than the control mice, which had been inoculated with only 10(2) live L1210 cells. This result is in contrast with the survival of mice primed with 10(3) live L1210 cells; 40% of these mice were cured and they survived for a mean 18.5 days. Transferred spleen and peritoneal cells harvested 11 or 21 days, respectively, after the inoculation of donor mice with live L1210 cells prolonged the life-span of the recipient mice. Spleen and peritoneal cells of primed mice harvested 11 days after live L1210 cell inoculation were treated with anti-mouse brain-associated T cell (BAT) antisera plus complement or complement alone and transferred ip to the mice. Spleen and peritoneal cells treated with complement alone prolonged the life-span of the recipients significantly, while effector cells treated with anti-BAT antisera and complement did not. Results indicated that the antitumor effector cells in the spleen and peritoneal cavity of the donor mice were T cells. (17 Refs)

42. IMMUNOGENICITY, MACROPHAGE SENSITIVITY, AND THERAPEUTIC RESPONSE TO C. PARVUM OF FIBROSARCOMAS INDUCED IN C. PARVUM-TREATED AND UNTREATED MICE.

Woodruff M, Forbes G, Gordon J
Medical Res. Council, Clinical and Population Cytogenetics Unit, Western General Hosp., Edinburgh EH4 2XU, Scotland
Cancer Immunol Immunother; 12(3):255-258 1982

Tumors which developed after injection of methylcholanthrene (MC) to Corynebacterium parvum (CP)-treated mice or implantation of MC-impregnated discs in untreated mice were studied in adult (17-22 g) female mice of strains CBA and BALB/c. Origin and properties of tumors are presented. All the tumors tested showed some degree of sensitivity in vitro to the cytotoxic effect of CP-activated macrophages (Mphi) in effector-target cell ratios down to 5 :1; many were highly sensitive at these ratios and also showed varying degrees of sensitivity at a ratio of 2.5 : 1 (the lowest ratio tested). A 10-fold increase in the concentration of arginine in the medium made no significant difference to the score. No correlation between the therapeutic response of a tumor to CP in vivo and its sensitivity to CP-activated Mphi in vitro was observed, nor any evidence was noted that either of these parameters was influenced by repeated administration of CP during the period of carcinogenesis or by whether the carcinogen was administered in solution or as crystals on a Millipore disc. Tumors which developed after injection of a small (0.1 mg) dose of MC in mice given repeated injections of CP had a significantly higher immunogenicity index than those which developed in mice which did not receive CP. A suggestion of similar effect after the injection of 0.5 mg MC was observed, but the difference was not statistically significant. (7 Refs)

43. INCREASE OF THE LIFESPAN AND DECREASE OF THE INCIDENCE OF TUMORS IN C3H/SN MICE TREATED WITH POLYPEPTIDE FACTORS FROM THE THYMUS GLAND AND PINEAL BODY.

Anisimov VN, Morozov VG, Khavinson VKh
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Dokl Akad Nauk SSSR; 263(3):742-745 1982

To evaluate the possible relationship between the aging and the state of immunity, female C3H/Sn mice were given injections of the polypeptide factors from the thymus (thymarin), pineal body (epithalamin) or from the anterior hypothalamus. The animals were followed up until the natural death. Prolonged administration of thymarin and epithalamin increased the lifespan of C3H/Sn mice by 2.5 and 3.5 mo, respectively. Administration of the polypeptide factors from the anterior hypothalamus decreased the lifespan by 2.5 mo. Thymarin and epithalamin slowed down the rate of aging. The incidence of mammary gland carcinomas in control C3H/Sn mice was 66.7%, compared with 24.0% after thymarin administration, 31.8% after epithalamin administration, and 38.9% after administration of the extract of the anterior hypothalamus. The mice treated with thymarin were free of leukemia, while 14.3% of the control mice developed leukemia. The specific antitumor effect of thymarin and epithalamin was associated with stimulation of cellular immunity: the indices of blast-transformation reaction in 9 mo old mice treated with thymarin and epithalamin were by 97% and 143%, respectively, greater than those in controls. (15 Refs) (In RUS)

44. INDUCTION OF ANTI-TUMOR CELL-MEDIATED IMMUNITY BY LOCAL IRRADIATION AGAINST TRANSPLANTED TUMOR.

Suda K
Dept. Neurosurgery, Kyoto Univ. Medical Sch., Kyoto, Japan
Nippon Geka Hokan; 51(1):59-69 1982

When C57BL/6 mice were locally irradiated with 60Co (1,000 or 1,500 rad) 10 days after intracerebral transplantation of methylcholanthrene-induced 203-glioma, survival rate was markedly increased (LD50, 4.5 wk for 1,000 rads, and 6.5 wk for 1,500 rads), compared to nonirradiated tumor-bearing mice (2.5 wk). Tests showed increased killer activity of spleen cells, reaching a maximum at 10 days after irradiation. Necrosis of tumor tissue was found. The killing activity was markedly reduced when the spleen cells were treated with anti-Thy 2 antibody, anti-BAT antiserum, and complement, suggesting the involvement of killer T cells. The sensitized spleen cells reacted well with Concanavalin A as well as to C cell growth factor (TCGF). Attempts to establish a murine glioma antigen-specific cytotoxic T cell line using TCGF was unsuccessful, because the killer activity diminished with the number of passages. (47 Refs) (In JPN)

45. H2D END DIFFERENT ALLOGRAFT INDUCE THE ANTI-TUMOR RESISTANCE IN VITRO IN SYNGENEIC MICE.

Chigira M, Nagase M, Maebara S, Watanabe H, Yabata N, Udagawa H, Takenichi Y
Dept. Orthopedics, Gunma Univ., Maebashi, Gunma, Japan
Nippon Seikeigeka Gakkai Zasshi; 55(9):1105-1106 1981

Live spleen cells 2 x 10(7) from C57BL/10 (B10) mice [H-2 congenic B10D2, B10A, B10BR, B10A (4R), and B10A(5R)], non-B10 AKR, and C3H/He mice, were allografted ip into A/J mice. Ten days later, fibrosarcoma S1509a cells induced by methylcholanthrene, or non-cross reacting fibrosarcoma S713a cells were inoculated subcutaneously. Frequency of establishment of antitumor resistance was high in B10BR, AKR, and C3H/He having k cell H-2 haplotype. The frequency was 40% in B10 with b H-2 haplotype, and none was observed when B10D2, d H-2 haplotype was used. When B10A(4R) and B10A(5R) were used, the frequency was 20% in B10A(4R) and none was found in B10A(5R). S713 a cells induced antitumor resistance at 5 x 10(3) inoculum but no tumor specificity was observed. No antitumor resistance was noted when tumor cells were inoculated 4 wk after allograft. Cell-mediated cytotoxicity test showed that the phenomenon was not due to the activity of the killer T cell. Activity of natural killer cells was not found either. (no Refs) (In JPN)

46. CELLULAR IMMUNITY TO ENCEPHALITOGENIC PEPTIDE IN TUMOR-BEARING MICE.

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Dept. Microbiology, Univ. Queensland, St. Lucia, Brisbane Q. 4067, Australia

Br J Cancer; 45(5):754-761 1982

Mice bearing a methylcholanthrene-induced tumor were tested for their cell-mediated reactivity to the experimental allergic encephalomyelitis (EAE) peptide of human myelin basic protein (MBP) in the leukocyte adherence inhibition (LAI) test. Tested over a range of peptide concentrations, peritoneal cells (PC) from tumor-bearing mice exhibited optimal adherence inhibition at 640 ng/ml; PC from normal and parasite-infected mice were unreactive. The EAE peptide also stimulated PC from tumor-bearing mice in the E-rosette augmentation (ERA) test and in the macrophage migration inhibition (MMI) test. MMI appeared to be the most sensitive assay, in that significant reaction at peptide concentrations well below those giving significant LAI and ERA. LAI reactivity to the peptide was detected 5 days after tumor transplantation, and continued to be detectable even with very large tumors. In vitro assays were confirmed by demonstration of EAE peptide recognition in vivo, in tumor-bearing and tumor-excised mice, using the delayed-type hypersensitivity reaction. The present experiments demonstrate an antigenic determinant in murine tumors, similar to the well-characterized EAE peptide of human MBP, and establish an animal model for study and characterization of common tumor-associated antigens. (Author abstract) (46 Refs)

47. DISEASE-RELATED LYMPHOCYTE CYTOTOXICITY IN RATS BEARING TRANSITIONAL CELL CARCINOMA OF BLADDER. EFFECT OF IMMUNOMODULATORS.

Moroz C, Madgar I, Twig S, Lindner A, Many M

Beilinson Medical Center, Rogoff-Wellcome Medical Res. Inst., Petah-Tikva 49100, Israel

Int J Cancer; 29(6):667-672 1982

Blood lymphocytes from rats bearing transitional cell carcinoma (TCC) of the bladder were studied for their cytotoxicity in vitro against xenogeneic YAC-1 target and against syngeneic TCC cells. Control lymphocytes were obtained from age and sex-matched syngeneic rats. The following differences were observed: (1) lymphocytes from TCC-bearing rats were cytotoxic to syngeneic TCC target cells whereas those from control rats were not; (2) lymphocytes from TCC-bearing and control rats were cytotoxic to NK sensitive YAC-1 cells; however, NK cells from TCC-bearing rats were more adherent to nylon wool-columns than NK cells from control rats. The adherent and non-adherent cells from TCC-bearing rats were both cytotoxic to syngeneic TCC target cells. Levamisole treatment of effector cells from TCC-bearing rats did not affect the NK activity, yet it increased the cytotoxicity of non-adherent cells on TCC target cells. Treatment of the adherent cells with poly-I:poly-C increased slightly their NK activity on YAC-1 cells and their anti-TCC cytotoxicity. However, a marked increase in the cytotoxicity by both adherent and non-adherent cell fractions was observed on TCC target cells pretreated with poly-I:poly-C. A disease-related cytotoxicity of lymphocytes from rats bearing TCC has been observed. Treatment of TCC target cells with poly-I:poly-C increased their susceptibility to lysis by the activated effector cells. (Author abstract) (33 Refs)

48. CELL-MEDIATED AND HUMORAL IMMUNE RESPONSES OF RATS DURING THE PROGRESSION OF PRIMARY AVIAN SARCOMA VIRUS-INDUCED INTRACEREBRAL GLIOMAS (MEETING ABSTRACT)

Woosley RE, Watkins PJ, Mahaley MS

No affiliation given

1982 Annual Meeting of the American Association of Neurological Surgeons, April 25-29, 1982, Honolulu, Hawaii. American Association of Neurological Surgeons 234 pp., 1982.

The avian sarcoma virus-induced glioma tumor model in the Fischer 344 rat has shown many parallels to the human glioma response. A longitudinal study of the specific immune responses of this tumor model has been studied using an in vitro microcytotoxicity assay monitoring cellular, humoral and antibody-dependent cytotoxicity. These studies were carried out to identify if and when an immune response might occur as the animal developed his tumor so that these responses might be manipulated in future therapeutic protocols. Tumor-bearing animals and their age-matched controls were sacrificed and studied every two weeks, from three to twenty-five weeks after they had been injected intracereberally with avian sarcoma virus at age day five. Other animals were immunized with target tumor cells to serve as an internal cytotoxicity control. Specific cellular (average 12%), humoral (average 5%) and antibody-dependent (average 11%) cytotoxicity of the tumor-bearing animals was not significantly different from their age-matched controls averaging 15%, 5%, and 13%, respectively. Immunized animals showed a significant specific cellular and humoral response averaging 30% and 39% respectively. (no Refs)

49. REGULATION OF LYMPHOCYTE TRANSFORMATION RESPONSES TO PHYTOHAEMAGGLUTININ, CONCANAVALIN A OR LIPOPOLYSACCHARIDE BY NORMAL SERUM.

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Ann Immunol (Paris); 133C(1):69-82 1982

Guinea-pig spleen lymphocytes were stimulated by phytohemagglutinin (PHA), Concanavalin, and lipopolysaccharide (LPS) in culture medium devoid of any serum. Homologous and autologous serum effected blastogenic responses induced by PHA, Con A, and LPS. Diluted serum enhanced thymidine uptake with a maximal enhancing effect for a 1/1,600 dilution. Addition of undiluted homologous serum depressed PHA-induced lymphoproliferation. The optimal mitogenic PHA dilution fluctuated in a narrow range no matter what serum concentration was used. In Con-A induced lymphocyte transformation, the addition of serum enhanced thymidine uptake. The optimal mitogenic concentration of Con A was observed to rise in the presence of increasing amounts of serum. LPS-induced blastogenesis was depressed by homologous serum, and high concentrations were more inhibitory than low ones. There was no evidence that serum interfered with LPS. Diluted serum appeared to have opposite effects on B- and T-cell mitogenesis. T-cell blastogenesis was enhanced whereas B-cell blastogenesis was depressed. It is suggested that the results could be explained by the interaction of serum with the membrane of lymphocytes stimulated with ConA, PHA, or LPS. (19 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

50. MECHANISMS OF TUMOR CELL LYSIS BY NATURAL KILLER CELLS.

Goldfarb RH, Timonen T, Herberman RB, Hibbs J, Henkart P

Cancer Metastasis Res. Group, Dept. Immunology and Infectious Disease, Pfizer Central Res., Groton, CT, 06340

Adv Exp Med Biol; 146(82):403-421 1982

Mechanisms of immune lysis, requirements for effector cell-target cell contact for natural killer (NK) mediated killing, role of neutral serine proteases in killer cells lysis of target cells and in NK cell-mediated cytolysis, phospholipases in NK mediated cytolysis, possible role of superoxide or other reactive oxygen species in lysis by NK cells and lymphotoxins in NK cell-mediated cytolysis, and possible inter-relationships among lytic mechanisms are discussed. More definitive evidence for a role of a particular biochemical event in cytotoxicity would not necessarily indicate that the mechanism is the primary, final, or sole event. (69 Refs)

51. STIMULATION OF NATURAL CYTOTOXIC ACTIVITY IN MIXED CELL CULTURES AND BY CULTURE SUPERNATANTS CONTAINING INTERFERON.

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Immunology; 46(2):401-409 1982

We have previously demonstrated that lymphocyte preparations cultured for 5 days with a number of different mitomycin-C-treated lymphoid cell lines showed increased non-specific (NK-like) cytotoxic activity. We have now examined the activity induced in T- and B-cell-enriched responder populations, prepared by sheep red blood cell (SRBC) rosette separation, and found that increased cytotoxic activity was present mainly in the T-cell-enriched fraction. To investigate whether soluble factors were involved in the mediation of enhanced cytotoxicity, freshly isolated effector cell populations before measurement of cytotoxicity against K562 cells. Effector cells pretreated with supernatants from mixed cell cultures incubated for 2-6 days showed increased cytotoxic activity, the greatest activity being obtained with supernatants from 4 and 5 days co-cultures. Increased activity was observed when effector cells were pretreated for 2, 4 and 18 hr with supernatants from mixed cell cultures, regardless of the nature of the stimulator cell (T- and B-cell derived lines, K562 and normal allogeneic lymphocytes). Active supernatants were produced by T-cell-enriched, but not B-cell-enriched responder populations. Supernatants from mixed cell cultures were also examined for the presence of interferon (IFN) and in general, those mediating large increases in cytotoxic activity also contained significant anti-viral activity. The IFN detected was not neutralized by antiserum to IFN-beta but was partly neutralized by antiserum to IFN-alpha. pH 2 treatment also removed part of the activity while a combination of pH 2 and anti-alpha completely neutralized the activity suggesting the presence of IFN-gamma and IFN-alpha. The candidacy of IFNs as mediators of enhanced cytotoxicity in this system is discussed. (Author abstract) (39 Refs)

52. POLYENZYMATIC ACTIVATION OF CELLULAR HYDROLASES INDUCED BY INTERFERON: ITS ROLE IN THE CYTOLYSIS PROCESSES AND IN OTHER MANIFESTATIONS INDUCED BY INTERFERON.

Zagury D, Maziere JC, Morgan D, Fouchard M, Gagne I, Hosli P

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C R Acad Sci [III] (Paris); 294(4):197-202 1982

Experimental results are presented which indicate that treatment of human effector T cells with interferon (IFN) brings about activation of hydrolytic enzymes in the T cells and cell-mediated cytolysis (CMC) of susceptible target cells; thus the treatment IFN of human effector T cells with IFN induced CMC against K562 target cells, with a concomitant increase in hexosaminidase and acid phosphatase. IFN treatment of L-929 cells similarly induced CMC activity and increased hydrolytic enzyme activity. (17 Refs) (In FRE)

53. INTERFERON INHIBITS PWM INDUCED B CELL DIFFERENTIATION BUT NOT ONSET OF PROLIFERATION.

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Leuk Res; 6(2):221-229 1982

Results of a test, using pokeweed mitogen (PWM) driven human lymphocyte system to elicit an in vitro humoral response are reported. The net DNA synthesis by PWM stimulated cells was reduced by approx 40% in the presence of interferon (INF) after 96 and 144 hr of culture. The presence of INF resulted in reduced net synthesis of DNA, indicating reduced net cell proliferation due to INF. The distribution of cells with respect to the G1/0-, S-, and G2 + M-cell cycle phases was similar in PWM stimulated cell cultures with or without INF. INF treated cells initiated DNA synthesis at the same time as untreated cells. The presence of INF, thus, did not affect the minimum transit from G0 to S. No difference in the population size was observed for cells in the presence or absence of INF until after 48 hr. However, the size of INF treated populations thereafter was persistently less. This is consistent with the INF induced reduced proliferation. The smaller population size of INF exposed populations is attributable to the reduction in proliferation rate relative to the loss rate. The rates of PWM induced proliferation by T cells and non-T cells were approx equal and reduced similarly in the presence of INF. The observed fraction of the population composed of T cells remained stable up to 144 hr for both cells treated and not treated with INF. The enrichment in the relative number of plasmacyte producing either kappa or lambda light chain antibody, due to PWM induced B cell differentiation, was reduced by INF. The observed reduced protein synthesis rate corroborates the reduced enrichment of immunoglobulin producing cells due to INF. (28 Refs)

54. ANTI-TUMOR CYTOSTATIC AND CYTOTOXIC PROPERTIES OF PERITONEAL CELLS OF CONVENTIONAL AND GERM-FREE MICE, STIMULATED OR NOT WITH 'CORYNEBACTERIUM PARVUM'.

Fray A, Moreau C, Thobie N, Ducluzeau R
Laboratorie de Pathologie Experimentale, Faculte Necker-Enfants-Malades, 75730 Paris, France
Ann Immunol (Paris); 133C(1):33-43 1982

Conventional mice (BALB/C males) treated with Corynebacterium parvum showed significant increases in the number of peritoneal cells. When germ-free mice (BALB/C males and females) were injected with C parvum, there was no significant modification in the number of peritoneal cells. The percentage of adherent cells increased significantly (p greater than 0.02) in conventional mice but remained constant in the germ-free mice. After treatment with C parvum, all the conventional and germ-free mice presented equivalent cytostatic properties against YC8 tumoral target cells. In conventional mice, nonactivated cells had a significant cytostatic effect (42%) on K BALB fibroblasts only when the ratio of effector cells to target cells was 40. The treatment of mice with C parvum significantly increased the cytostatic effects (97%) of effector cells. In germ-free mice, the cytostatic properties were from 51% to 84% with significantly higher cytostasis following activation with C parvum. In conventional mice, cytotoxic properties increased following activation with C parvum but in germ-free mice, cytotoxic properties were unchanged. It is suggested that variable microbial flora in conventional mice could cause variable cytotoxic and cytostatic reactions following treatment with C parvum. (24 Refs) (In FRE)

55. BACILLUS CALMETTE-GUERIN AS AN ANTITUMOUR AGENT: THE INTERACTION WITH CELLS OF THE MAMMALIAN IMMUNE SYSTEM.

Davies M
Inst. Genetics, Univ. Glasgow, Glasgow G11 5JS, Scotland
Biochim Biophys Acta; 651(2/3):143-174 1982

The proposal that BCG is a nonspecific potentiator of the immune system is examined with evidence for the interaction of BCG with identifiable cell types. Interaction of BCG with lymphoid cells (T cells, B cells, killer cells, and natural killer cells) and macrophages is reviewed. A hypothetical model for the stimulation of T-cell-mediated immunity by BCG as an example of BCG/mammalian immune cell interaction is presented. (279 Refs)

56. THE EFFECTS OF RETINOIC ACID AND A TUMOR PROMOTER, 12-O-TETRADECANOYLPHORBOL-13-ACETATE, ON LYMPHOCYTE PROLIFERATION.

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Dept. Microbiology, Cell Biology and Biophysics, Pennsylvania State Univ., University Park, PA, 16802
Carcinogenesis; 3(4):409-413 1982

The tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) inhibits DNA synthesis in allogenic, mixed cultures of bovine lymphocytes. Retinoic acid, an antagonist of TPA in in vivo skin promotion, was tested for its ability to counteract the effect of TPA on lymphocyte proliferation. Retinoic acid or related compounds, retinol or retinol acetate, did not reverse or prevent the inhibitory effect of TPA. Instead retinoic acid also inhibited DNA synthesis in mixed lymphocyte cultures. On the av, about 8 uM retinoic acid inhibited the mixed lymphocyte response by 50%. The mitogenic response of lymphocytes to phytohemagglutinin (PHA) was also inhibited by retinoic acid. The degree of inhibition depended both on the concentration of PHA and of retinoic acid. Therefore, in regard t bovine lymphocytes, retinoic acid depresses DNA synthesis i both allogenic and lectin stimulated responses. Such suppression should be taken into account in the use of retinoic acid i chemotherapy. (Author abstract) (29 Refs)

57. AUGMENTATION OF SPONTANEOUS MACROPHAGE-MEDIATED CYTOLYSIS BY EOSINOPHIL PEROXIDASE.

Nathan CF, Klebanoff SJ
Rockefeller Univ., New York, NY, 10021
J Exp Med; 155(5):1291-1308 1982

Eosinophil peroxidase (EPO) adhering to LSTRA, TLX9, and NK lymphoma and P815 mastocytoma cells markedly potentiated tumor cell lysis by H2O2. The LSTRA cells lysed in the presence of halide, but the other cells lysed in the order TLX9 greater than P815 greater than NK without additional halide. EPO catalyzed the lysis of tumor cells by H2O2 released spontaneously from mouse peritoneal activated macrophages in the absence of exogenous triggering agents. This peroxidase-dependent cytotoxicity occurred in a complex, serum-containing tissue culture medium without further addition of halides. The medium could support replication of TLX9, P815, and P388 cells at approx the same rate as in the mouse peritoneal cavity. TLX9 lymphoma cells became approx 15-fold more sensitive after exposure to EPO; NK lymphoma cells became up to 76-fold more susceptible after similar treatment. Spontaneous lysis of EPO-coated tumor cells was rapid (50% at 2 hr at a macrophage/tumor cell ratio of 6/1), but control target cells were almost completely spared during an 8 hr incubation with activated macrophages. Macrophages and eosinophils may cooperate in exerting extracellular toxicity in tumor beds, sites of parasitic infestation, or other foci of inflammation. (51 Refs)

58. LYMPHOKINE-ACTIVATED KILLER CELL PHENOMENON. LYSIS OF NATURAL KILLER-RESISTANT FRESH SOLID TUMOR CELLS BY INTERLEUKIN-2-ACTIVATED AUTOLOGOUS HUMAN PERIPHERAL BLOOD LYMPHOCYTES.

Grimm EA, Mazumder A, Zhang HZ, Rosenberg SA
Surgery Branch, NCI, Bethesda, MD, 20205
J Exp Med; 155(6):1823-1841 1982

It had previously been reported that peripheral blood leukocytes from cancer patients could be activated in culture by preparations of interleukin-2 (IL-2), resulting in the development of effector cells cytotoxic for autologous fresh solid tumors in short-term 51chromium release assays in greater than 90% of cancer patients tested. A study is presented which further characterizes the IL-2-induced antitumor cytotoxicity phenomenon. Major features of the lymphokine-activated killer (LAK) system include: (1) LAK lysing of natural killer (NK)-resistant fresh solid tumor cells; (2) LAK could be generated by a 2-3 day culture in IL-2 containing supernatants, from either allogeneic or autologous sources; (3) immune interferon was not the primary stimulus responsible for LAK; (4) neither precursors nor LAK effectors were adherent cells; (5) LAK precursors were found in NK-void thoracic duct lymphocyte populations, as well as in peripheral blood lymphocytes (PBL) of normal subjects and PBL of cancer patients; (6) LAK development was radiation sensitive; and (7) LAK effectors expressed the serologically defined phenotype of T cells. These findings suggested that the human LAK phenomenon is distinct from the NK and cytotoxic T lymphocyte systems. (44 Refs)

59. INHIBITORY EFFECTS OF VARIOUS OXYGENATED STEROLS ON THE DIFFERENTIATION AND FUNCTION OF TUMOR-SPECIFIC CYTOTOXIC T LYMPHOCYTES.

Spangrude GJ, Sherris D, Daynes RA
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Transplantation; 33(5):482-491 1982

These studies were undertaken to determine the effect of various oxygenated sterols (representing a number of known cholesterol-derived photoproducts) on the generation (afferent) and function (efferent) of cytotoxic T lymphocytes (CTLs). Cell-mediated immune responses which result in the generation of both alloantigen-specific and syngeneic tumor-specific CTLs were evaluated. The results of our studies established the following points: (1) the afferent phase of an immune response is particularly sensitive to the effects of some cholesterol photoproducts while other oxidized sterol derivatives, known to exist in skin following UV light (UVL) exposure, have minimal influence on the generation of CTL responses; (2) the only known carcinogenic photoproduct of cholesterol (cholesterol alpha-oxide) is a very weak inhibitor of lymphocyte function; and (3) presentation of oxygenated sterols via liposome membranes is 10-fold more effective than their administration in soluble form; (4) 25-hydroxycholesterol and 20alpha-hydroxycholesterol were found to be the most potent inhibitors, causing a parallel depression in lymphocyte proliferation, CTL activity, and endogenous sterol biosynthesis, and (5) 7beta- and 7alpha-hydroxycholesterol functioned in a unique manner, causing an abrogation of CTL activity without depressing proliferative responses and endogenous sterol biosynthesis to a significant degree. These studies represent the first time that an attempt has been made to evaluate a possible biochemical basis for immune suppression known to precede experimental UVL carcinogenesis. Our results suggest that some, but not all, of the oxidation products of cholesterol found in skin following UVL irradiation exert an influence on immune responses. Derivatives of cholesterol could be partially responsible for the alterations in immunological potential of the UVL-exposed host. The induced presence of an inhibitor of CTL differentiation or function at a time following UVL tumor emergence may play a role in this process by providing an early tumor escape mechanism. (37 Refs)

60. MAJOR HISTOCOMPATIBILITY COMPLEX (B): EFFECT ON THE RESPONSE OF CHICKENS TO A SECOND CHALLENGE WITH ROUS SARCOMA VIRUS.

Guyre PM, Zsigray RM, Collins WM, Dunlop WR
Dept. Microbiology, Univ. New Hampshire, Durham, NH, 03824
Poult Sci; 61(5):829-834 1982

Immunity to a second Rous sarcoma virus (RSV)-induced tumor in chickens with varying B blood group genotypes was investigated. Most B2/B2 hosts resisted development of tumor after a second RSV challenge, while all B5/B5 hosts developed tumors after both challenges. Tumor growth was not enhanced when tumorous chickens were rechallenged with RSV. When mixtures of RSV plus sera from uninoculated control chickens were inoculated into susceptible hosts, normal tumor induction resulted. Sera from chickens which complete regressed their primary tumors neutralized RSV, however. Regardless of B genotype, levels of serum IgG in F4 crosses at 0, 11, 14, and 21 days postinoculation did not differ significantly. Both humoral and cell-mediated antitumor immunity may be important in resistance to early RSV-induced tumor growth. (15 Refs)

61. THE EFFECT OF CIS-DIAMMINEDICHLOROPLATINUM (II) ON IMMUNE FUNCTION IN VITRO AND IN VIVO.

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Cancer Immunol Immunother; 12(3):191-196 1982

Effects of cis-diamminedichlorplatinum(II) (cis-DDP) on a naturally occurring immune function, spontaneous monocyte-mediated cytotoxicity (SMMC) are reviewed. Cis-DDP selectively inhibits DNA rather than RNA or protein synthesis in eukaryotic and prokaryotic cells. Cis-DDP is mutagenic, teratogenic, and carcinogenic; and it can induce lysogenic DNA viruses to lyse their host cells. In vitro treatment of human mononuclear cells with concentrations of cis-DDP as low as 10(-9) M for 15 min will enhance SMMC. Cis-DDP specifically and selectively stimulated the monocyte killer itself rather than inhibiting the lymphocyte suppressor function. Thus, at a concentration 1,000-fold lower than that needed to create detectable DNA damage or produce cytotoxic effects in cultured malignant cells, cis-DDP stimulated a naturally-occurring immune function. Eight patients with ovarian cancer were studied and their SMMC prior to successive courses of chemotherapy was sequentially determined. In each of the seven evaluable patients their cytotoxic function increased three-fold during combination chemotherapy that contained cis-DDP as one agent. Six of these seven patients responded with measurable tumor regression. Data indicated that cis-DDP has a direct tumoricidal action and enhances a naturally occurring immune function causing destruction of tumor by the host's own activated defense system. Normal peripheral mononuclear leukocytes were treated with 10(-5) M cis-DDP for 1 hr and then the ability of these cells to respond to various mitogens (phytohemagglutinin, concanavalin A, pokeweed mitogen) and specific antigens (tetanus, diphtheria) was assayed by measuring their 3H-thymidine incorporation during the terminal 4 hr of the 3-or 6-day assay. No difference was observed in the ability of the cis-DDP-treated cells to respond to the mitogens or antigens. (50 Refs)

62. STIMULATION OF MURINE SPLENIC LYMPHOCYTES AFTER SKIN PAINTING WITH A TUMOR PROMOTER (MEETING ABSTRACT)

Schoof RA, Baxter CS
Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH
Toxicologist; 2(1):91 1982

The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) synergistically enhances the response of murine lymphocytes to T-cell mitogens but has very little mitogenic activity alone in vitro. In order to examine the effects of TPA in vivo, its interaction with Staphylococcus enterotoxin A (SEA), a recently reported in vivo T-lymphocyte mitogen, was investigated. Back skin of Balb/c mice was painted with 2, 6, or 10 ug of TPA in 100 ul of acetone twice weekly for two weeks. Twenty-four hours after the last dose 20 ug of SEA was administered retro-orbitally. Forty-eight hours after the SEA injection spleen lymphocyte mitogenic activity was increased in a dose-related manner, a 60% increase occurring at the highest (10 ug) dose. However, unlike its effects on lymphocytes in vitro, skin painting with TPA stimulated mitogenesis even when no other mitogen was present. Mitogenic activity in mice treated with TPA, but not with SEA, was approximately 50% of the levels induced in acetone-treated mice by injection of SEA. One application of 6 ug of TPA was sufficient to induce a two-fold enhancement of mitogenesis within 24 hours. Peak stimulation was reached between 48 and 72 hours after dosing. When mice received two weeks of TPA treatments, the maximum stimulation reached 48 hours after the last application was more than twice the maximum level achieved after one TPA application. An 8-fold enhancement of mitogenic activity was observed at that time. (no Refs)

63. THE EFFECT OF 12-O-TETRADECANOYL PHORBOL-13-ACETATE (TPA) ON THE ANTIBODY PRODUCING CAPABILITIES OF IN VITRO SENSITIZED SPLEEN CELLS (MEETING ABSTRACT)

Shopp G, White K, Munson A
Department of Pharmacology, Medical College of Virginia, Richmond, VA
Toxicologist; 2(1):93 1982

TPA affects several elements of the immune system and the study of the mechanisms of these effects may offer insight concerning its mechanism of action as a tumor promoter. This study examines the effect of TPA on the in vitro immunization of BDF1 mouse spleen cells to sheep red blood cells, as measured by the number of IgM antibody forming cells (AFC). The ED50 that suppressed AFC was between 7.7 x 10-10M and 7.7 x 10-9M; 7.7 x 10-8M resulted in complete inhibition. TPA did not significantly affect cell viability at these concentrations (trypan blue exclusion test). A time course study showed that the suppression seen was not due to a shift of the peak response day. When TPA was added on consecutive days, it inhibited AFC when added on days 0 and 1. Addition on day 2 resulted in 50% inhibition, whereas days 3 and 4 resulted in a 2.2 and 1.3 fold increase, respectively. These results suggest that TPA may be affecting the macrophage early in the immune response, considering the macrophage is important in the initial 48 hours. However, because of the enhanced response on day 3, other cell types such as the suppressor T-cell may also be affected. (no Refs)

64. MODE OF ACTION OF POLYETHYLENE GLYCOL 6000 IN POTENTIATING THE IN VITRO GENERATION OF ANTITUMOR CYTOTOXICITY BY MOPC-315 TUMOR BEARER SPLEEN CELLS.

Mokyr MB, Przepiorka D, Dray S
Dept. Microbiology and Immunology, Univ. Illinois at the Medical Center, Chicago, IL, 60612
Cancer Res; 42(7):2537-2543 1982

Some of the possible mechanisms by which polyethylene glycol (PEG) augments the ability of MOPC-315 tumor bearer spleen cells to mediate in vitro antitumor cytotoxicity were evaluated. The level of antitumor cytotoxicity obtained in 5-day cultures of tumor bearer spleen cell suspensions correlated inversely with the percentage of Trinitrophenol (TNP)-rosettable cells (presumably metastatic tumor cells) present in the spleen. The kinetics of decrease in the percentage of TNP-rosettable cells coincided with the appearance of antitumor cytotoxicity. In addition, PEG was shown to interfere with the ability of viable tumor cells to suppress the in vitro generation of antitumor cytotoxicity in normal spleen cells cultured with mitomycin C-treated tumor cells. However, the decrease in the content of TNP-rosettable cells and the concurrent increase in the level of antitumor cytotoxicity were not due to direct cytotoxic and/or cytostatic effects of PEG on tumor cells. Spleen cells cultured in the presence of PEG had an increased rate of [3H]thymidine incorporation and proliferation compared to spleen cells cultured in the absence of PEG. However, the PEG-induced decrease in the percentage of TNP-rosettable cells either preceded or occurred at the same time that PEG-induced increase in spleen cell number was observed. Therefore, spleen cell proliferation can at best explain only partially the PEG-induced decrease in the content of TNP-rosettable cells, and other mechanisms for the decrease must be considered. (Author abstract) (25 Refs)

65. LYMPH-DEPLETIVE ACTION OF VINCRISTINE ON LYMPHOID TISSUE OF RABBIT APPENDIX.

Bux P

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Acta Chir Ital; 38(1):127-132 1982

The lymph-depletive action of vincristine sulfate (VCR: 0.1 mg/kg iv qod for 2 wk) on the lymphoid tissue of the appendix was studied in 10 male and female rabbits. Widespread destruction of lymphoid cells was observed. The findings indicate the lymph-depletive action of VCR and support its possible suppressive action on cellular immunity. (15 Refs) (In ITA)

66. IN VITRO EFFECT OF CIMETIDINE ON HUMAN CELL-MEDIATED CYTOTOXICITY. I. INHIBITION OF NATURAL KILLER CELL ACTIVITY.

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Cell Immunol; 69(1):1-12 1982

The effect of cimetidine on human natural killer cell activity against K562 myeloid cells was studied. A bimodal inhibitory dose-related effect was found, as the result of the interaction of the drug with both target and effector cells. Cimetidine inhibits natural killer effector cells at very low molar concentrations and both effector and glass-adherent cells exerting suppressor function of natural killer cell activity at intermediate concentrations. High doses of the drug, besides affecting the effector cell subpopulations, seem to trigger an active protective mechanism in the target cells, thus resulting in the total abrogation of natural killer cell activity. (Author abstract) (37 Refs)

67. TUMOR CELL DIFFERENTIATION MODULATES SUSCEPTIBILITY TO NATURAL KILLER CELLS.

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Cell Immunol; 69(1):122-127 1982

Induced differentiation in three human cell lines altered their sensitivity specifically to human natural killer (NK) cells by affecting their expression of NK target antigens. Differentiation of HL-60, a promyelocytic leukemia cell line, and the erythroleukemic cell line K562 was accompanied by a concomitant decrease in susceptibility to NK-mediated lysis whereas induction of MeWo melanoma cells resulted in an enhanced sensitivity to lysis. Our findings suggest that target cell susceptibility to NK-mediated lysis may in part be dependent on the stage of differentiation of the tumor cell target. (Author abstract) (23 Refs)

68. LOSS OF SURFACE-BOUND ANTIBODY ACCOMPANYING THE ANTI-COMPLEMENTARY MODULATION OF LEUKEMIC B CELL IMMUNOGLOBULIN: CONTRASTING EFFECTS OF ANTIBODIES DIRECTED AGAINST IDIOTYPIC AND CONSTANT REGIONS.

Gordon J, Anderson VA, Stevenson GT
Dept. Tumor Biology, Karolinska Inst., Box 60400, S-104 01 Stockholm, Sweden
J Immunol; 128(6):2763-2769 1982

Guinea pig L2C leukemia lymphocytes display at their surfaces monoclonal IgM, which when complexed with antibody undergoes rapid redistribution and variable endocytosis. One consequence of this is that the cells can prove resistant to lysis by complement subsequently added to the system, a process termed here anti-complementary modulation. We studied quantitatively the extent of antibody loss accompanying the modulation by radioimmunolabeling the cell surfaces with 125I-Fab'-gamma fragments from an anti-antibody. Antibody directed against the constant region of the IgM light chain (anti-lambda) gave modulation effective against syngeneic (guinea pig strain 2) complement that closely paralleled the disappearance of anti-lambda from the cell surfaces. Antibody directed against the idiotypic region of the light chain (anti-Id) was as effective as anti-lambda in modulating against syngeneic complement. However, the bulk of the anti-Id was seen by radioimmunolabeling to persist on the surfaces of the resistant cells, even after prolonged exposure at 37 C, and was shown by immunofluorescence to be in a patched configuration. In contrast to the results with syngeneic complement, modulation effective against rabbit complement appeared to have an absolute requirement for clearing of the antibody: thus anti-lambda could modulate, anti-Id could not. The differences observed between anti-lambda and anti-Id could not be accounted for by differences in their isotypic (Ig subclass) composition nor by the numbers of antibody molecules bound. Studies with directly fluoresceinated and 125I-labeled and anti-lambda revealed endocytosis rather than shedding was the major route of antibody loss from the cell surfaces over the period of anti-complementary modulation. The findings are discussed in relation to mechanisms that enable leukemic B lymphocytes to escape destruction when confronted by antibody and complement. (Author abstract) (32 Refs)

69. IN VITRO DEPRESSION OF HUMAN LYMPHOCYTE MITOGEN RESPONSE (PHYTOHAEMAGGLUTININ) BY ASBESTOS FIBRES.

Barbers RG, Shih WW, Saxon A
Dept. Medicine, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Clin Exp Immunol; 48(3):602-610 1982

Asbestosis is a fibrotic lung disease associated with chronic inhalation of asbestos dust. The response of peripheral blood mononuclear cells (PBM) to phytohemagglutinin (PHA) in asbestosis patients has been reported to be impaired, suggesting a disturbance in the cell-mediated response of chronically exposed individuals. We demonstrated that PHA responses of normal PBM are also depressed when exposed to various forms of asbestos fibers in vitro. Furthermore, we showed the primary effect of the fibers to be on lymphoid (non-adherent) populations rather than monocytes (adherent cells). Exposure as brief as 1 hr affected the subsequent PHA response of the cells. This effect did not appear to involve suppressor cell activation nor was it mediated by soluble factors. Our findings therefore offer an explanation for the alterations in the cellular immune response observed in humans as a result of lymphoid cells coming into transient contact with inhaled asbestos fibers residing in the lung. (Author abstract) (20 Refs)

70. ENHANCEMENT OF NATURAL CYTOTOXICITY IN TUMOR-BEARING ANIMALS (MEETING ABSTRACT)

Droller MJ, Gomolka D
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We previously observed in a 51 Chromium release assay that lymphocyte natural cytotoxicity in a carcinogen-induced model of bladder cancer was depressed within six weeks after the onset of ingestion of the carcinogen (FANFT). Lymphocyte blastogenesis was not effected during this depression and the generation of suppressor lymphocytes could not be demonstrated. Neither elimination of monocytes from lymphocyte preparations nor inhibition of macrophage prostaglandin E2 production enhanced lymphocyte cytotoxicity, and addition of macrophages did not further depress lymphocyte cytotoxicity. The implication of natural cytotoxicity in immune surveillance and the prevention of tumor progression, however, prompted us to determine whether the depressed cytotoxicity seen in tumor-bearing animals could be enhanced through either in vitro or in vivo manipulations. First, we demonstrated that natural cytotoxicity could be directly enhanced by interferon, often to exceed levels seen in control lymphocytes. Moreover, inducers of interferon production, such as poly I:C, could induce a similar in vitro response. Correspondingly, in vivo treatment of control and tumor-bearing animals with poly I:C demonstrated similar enhancement of natural cytotoxicity. Correlation with tumor progression in this model demonstrated that enhancement of natural killer activity might be associated with inhibition of tumor growth especially when accomplished in conjunction with manipulation of in vivo prostaglandin production. (no Refs)

71. WHAT IS THE ROLE OF T-LYMPHOCYTE SURVEILLANCE IN NEOPLASTIC DISEASE?

Rothenberg E
Div. Biology, California Inst. Technology, Pasadena, CA, 91125
Am J Surg; 143(6):664-669 1982

The roles cytotoxic, helper, and natural killer T cells in neoplasia are described. Mechanisms by which the immune system defends against malignancy, the efficacy of T lymphocytes against neoplasia, and the possibility of therapeutically mobilizing the immune system against tumors are considered. Experimental and clinical results in studies of tumor immunology are reviewed. (53 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

72. VITAMIN D3 AND ITS METABOLIC PRODUCTS.

Abe E, Suda T
Dept. Biochemistry, Showa Univ. Sch. Dentistry, Tokyo, Japan
Nippon Rinsho; 39(9):119-122 1981

Vitamin D3 is converted into an active molecule, 1alpha,25(OH)2D3, which was unexpectedly found to induce differentiation of M1 cells (established from a myelocytic leukemic SL mouse) into macrophages and their precursor cells. The differentiation inducing ability of 1alpha,25(OH)2D3 was 100 times stronger than that of dexamethasone (DEX), a strong differentiation inducer, and matched the binding ability of the D3 derivative to the receptor protein in the cytosol fraction of the small intestine. (9 Refs) (In JPN)

73. MACROPHAGE ACTIVATION BY INTERFERON: DISSOCIATION BETWEEN TUMORICIDAL CAPACITY AND SUPPRESSIVE ACTIVITY.

Boraschi D, Soldateschi D, Tagliabue A
Lab. Immunopharmacology, Sclavo Res. Center, Via Fiorentina, 1, 53100 Siena, Italy
Eur J Immunol; 12(4):320-326 1982

Resident peritoneal macrophages (M phi) from untreated mice and inflammatory M phi induced by a sterile irritant were able to exert significant suppressive activity on lymphocyte functions. M phi-mediated suppression was evident in lymphocyte proliferation and in a proliferation-independent lymphocyte response (ie lymphokine production). The lymphokine macrophage-activing factor (MAF), which enhances tumoricidal capacity of inflammatory but not of resident M phi in vitro, was ineffective in modulating suppressive activity of both resident and inflammatory M phi. In contrast, a significant effect on M phi-mediated suppression was observed upon treatment with IFN-beta. In fact, suppression of lymphoproliferation and of lymphokine production by either resident or inflammatory M phi was significantly decreased or abolished by IFN-beta. Like MAF, IFN-beta was able to increase M phi cytotoxicity against tumor cells. Such an effect, however, was evident in both resident and inflammatory M phi, thus confirming different M phi activation mechanisms for MAF and IFN-beta. These data indicate that IFN-beta acts mainly on mature M phi, which thus appear as the major M phi type involved in suppression. The contrasting effects of IFN-beta on M phi suppression and on M phi-mediated cytotoxicity strongly suggest a dissociation between the two induction mechanisms of suppression and cytotoxicity. The in vivo relevance of these two IFN activities was demonstrated by treating mice with the potent IFN inducer polyinosinic polycytidylic acid (poly(I) . poly(C)). M phi from poly(I) . poly(C)-primed mice simultaneously showed enhanced tumoricidal activity and complete abolishment of suppressive capacity. (Author abstract) (38 Refs)

74. TUMOR-PROMOTING DITERPENE ESTERS PREVENT MACROPHAGE ACTIVATION AND SUPPRESS MACROPHAGE TUMORICIDAL CAPACITY.

Keller R, Keist R, Adolf W, Opferkuch HJ, Schmidt R, Hecker E
Arbeitsgruppe fur Immunbiologie, Institut fur Immunologie und Virologie, Universitat Zurich, CH-8032 Zurich, Switzerland
Exp Cell Biol; 50(3):121-134 1982

The efficacy of varied diterpene ester type tumor promoters in suppressing the acquisition as well as the manifestation of cytolytic activity by macrophages was investigated. These mechanisms, believed to be basic to natural antitumor resistance, were markedly suppressed not only by the phorbol ester, TPA, but also by several other tumor promoters of the polyfunctional diterpene ester type covering tigliane, ingenane, and daphnane derivatives. The promoters were particularly effective in preventing the lymphokine-induced enhancement of natural cytolytic activity in resting macrophages. Moreover, the same promoters suppressed the manifestation of cytotoxicity by previously activated macrophages. Their influence on the effector phase was less pronounced than on the activation phase. In sharp contrast, typical solitary carcinogens of the polycyclic aromatic hydrocarbon type exerted little or no activity in the macrophage test systems. Since TPA had already been shown to suppress the natural killer activity in vitro and to abrogate host tumor resistance in vivo, the present findings lend further support to the interpretation that tumor promoters, apart from directly stimulating the outgrowth of transformed cells, may function via interference with natural antitumor effector systems. (Author abstract) (54 Refs)

75. IN SITU ACTIVATION OF TUMORICIDAL PROPERTIES IN RAT ALVEOLAR MACROPHAGES AND REJECTION OF EXPERIMENTAL LUNG METASTASES BY INTRAVENOUS INJECTIONS OF NOCARDIA RUBRA CELL WALL SKELETON.

Sone S, Fidler IJ
(c/o Fidler) Cancer Metastasis and Treatment Lab., NCI-Fredrick Res. Facility, P.O. Box B, Fredrick, MD, 21701
Cancer Immunol Immunother; 12(3):203-209 1982

Influence of systematically administered squalene-treated cell wall skeleton of Nocardia rubra (N-CWS) on the tumoricidal properties of rat alveolar macrophages (AM) and on levels of AM activation sufficient to eradicate established experimental pulmonary metastases of a syngeneic mammary adenocarcinoma was studied in specific pathogen-free inbred F344 (5-7 wk old) female rats. Significant and reproducible cytotoxicity was mediated by AM harvested from rats that had received N-CWS iv. Injection of N-CWS placebo did not render AM tumoricidal. Statistically significant levels of cytotoxicity were mediated by AM harvested from rats injected with more than 150 ug N-CWS. Reproducible maximal levels of tumor cytotoxicity were obtained with 300 ug N-CWS iv/rat; AM remained tumoricidal for 48-72 hr. In experiments where N-CWS was injected sc, ip, or iv, only AM from iv-injected rats were tumoricidal. Data agreed with previous results showing that the activation of macrophages at a given anatomical site requires that the activating stimulus be delivered to the macrophages. All the rats treated with Hanks' balanced salt solution or N-CWS placebo preparations had developed lung tumor colonies (LTC). In contrast, 11/13 treated rats with N-CWS were free of visible LTC. Data suggested that established parenchymal pulmonary micrometastases could be eradicated by iv injections of N-CWS. (29 Refs)

76. DESTRUCTION OF MBT-2 TUMOR CELLS IN VITRO BY MACROPHAGES ACTIVATED WITH MACROPHAGE ACTIVATION FACTOR PRODUCED BY A T-CELL HYBRIDOMA (MEETING ABSTRACT)

Ratliff TL, Shapiro A, Catalona WJ
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We have developed a T-cell hybridoma (F133) that produces macrophage activation factor (MAF) after mitogen stimulation. MAF induces macrophage-mediated tumoricidal activity against MBT-2 and EMT-6 tumor cells by peritoneal macrophages from thioglycolate injected C3H/Anf mice. F133 was developed by alloantigen sensitization of C3H/HeJ mice with 10(7) C57B/6 splenocytes. Five days later C3H/HeJ splenocytes were harvested and fused with AKR-derived BW5147 thymoma cells by the drop wise addition of 50% polyethylene glycol. F133 supernatants were shown to contain MAF, migration inhibition factor and a factor that suppressed the plaqueformig response of splenocytes to sheep erythrocytes but not lymphotoxin, interleukin II or interferon. Both concanavalin A (Con A) and phytohemagglutinin (PHA) induced MAF production by F133. Time-course and dose-response experiments showed that maximal concentrations of MAF were present 48 hours after stimulation with either 1.5 ug/ml Con A or 6 ug/ml PHA. Physicochemical characterization of F133 MAF showed that heating at 100 C for 30 minutes abolished MAF activity while 56 C for 30 minutes or 100 C for 2 minutes had no effect. Treatment of F133 MAF at pH 4.0 or pH 10 abrogated activity while pH 6.0 and pH 8.0 had little effect. Also, pretreatment of F133 MAF with either trypsin or chymotrypsin inactivated MAF activity. (no Refs)

77. EXPERIMENTAL STUDY OF FUNCTIONAL STATE AND ENZYMATIC STRUCTURE OF PULMONARY ALVEOLAR MACROPHAGES AFTER PERORAL EXPOSURE TO DIMETHYLNITROSAMINE.

Merkur'eva RV, Litvinov NN, Aulika BV, Mukhambetova LKh, Bushinskaia LI, Dolinskaia SI, Iakimova ER, Konstantinova IN, Votiakov AV
Lab. Biochemistry, A. N. Sysin Inst. General and Community Public Health, Moscow, USSR
Biull Eksp Biol Med; 93(4):41-43 1982

Effect of peroral exposure to dimethylnitrosamine (DMNA: 30 mg/kg) on pulmonary alveolar macrophages was studied in male random-bred albino rats. DMNA administration produced progressive decrease of the number of viable alveolar macrophages. The decrease of macrophage count was associated with the increase of activities of microsomal acetylesterase and lysosomal beta-glucuronidase and the decrease of activity of mitochondrial malate dehydrogenase. (8 Refs) (In RUS)

78. ANTITUMOR AND TOXIC PROPERTIES OF RETINOID C15.

Afanas'ev IuI, Nozdrin VI, Bakhshinian MZ, Samokhvalov GI, Vakulova LA, Iakovleva IM
Dept. Histology and Embryology, I. M. Sechenov First Medical Inst., Moscow, USSR
Biull Eksp Biol Med; 93(4):76-78 1982

Antitumor activity and toxicity of synthetic metabolite of vitamin A (retinoid C15) were studied in C57BL/6 mice with transplanted Lewis lung carcinoma and cervical carcinoma, and in CBA mice with transplanted stomach carcinoma. The animals received ip injections of retinoid C15 (0.2-1.6 mg, qod). Retinoid C15 was less toxic than retinoic acid (max permissible doses were 1.5 g/kg and 0.3 g/kg, respectively). Retinoid C15 inhibited the growth of transplanted tumors. Retinoid C15 did not inhibited the hematopoiesis and phagocytic activity of macrophages in tumor-bearing animals. (7 Refs) (In RUS)

79. THE CAPACITY OF ACTIVATED MURINE MACROPHAGES FOR AUGMENTED BINDING OF NEOPLASTIC CELLS: ANALYSIS OF INDUCTION BY LYMPHOKINE CONTAINING MAF AND KINETICS OF THE REACTION.

Marino PA, Adams DO
Dept. Pathology and Microbiology-Immunology, Duke Univ. Medical Center, Durham, NC, 27710
J Immunol; 128(6):2816-2823 1982

The capacity for augmented binding of tumor cells is an initial and necessary part of macrophage-mediated tumor cytotoxicity. To study the induction of binding capacity, we obtained FCS-elicited, inflammatory macrophages from C57BL/6J mice. Exposure of these macrophages to lymphokine(s) containing MAF induced augmented binding capacity in a dose-dependent fashion. Resident peritoneal macrophages did not respond to lymphokine, and endotoxin did not appreciably influence induction of binding. Maximum induction of binding required continuous interaction between macrophages and lymphokine for 6 to 10 hr. The conditions necessary for induction of binding closely paralleled those for induction of priming for cytolysis. Exposure of FCS-elicited macrophages from C3H/HeJ mice, although not of macrophages from A/J mice, induced augmented binding. The data suggest that the augmented capacity for binding tumor cells is induced by lymphokine(s) and that a major part of induction of priming for cytolysis by MAF is induction of such binding. (Author abstract) (27 Refs)

80. MACROPHAGE FUNCTIONAL STATUS AND NEOPLASIA.

Di Luzio NR
Dept. Physiology, Tulane Univ. Sch. Medicine, New Orleans, LA, 70112
Pathophysiology of the Reticuloendothelial System. Altura BMand Saba TM, ed. New York, Raven Press, 233 pp., 1981.

Macrophages and tumor surveillance, effects of stimulation and depression by glucan and palmitate on the reticuloendothelial system (RES), and morphologic and biochemical studies on tumor-macrophage interactions are discussed. The role of macrophages in the mediation of tumor cell surveillance and destruction is based on the observation that agents, such as BCG, Corynebacterium parvum, methanol extraction residue, and glucan, that enhance macrophage number and function increase resistance to tumor growth. (33 Refs)

81. EFFECTS OF CADMIUM, LEAD, AND ZINC ON MACROPHAGE-MEDIATED CYTOTOXICITY TOWARD TUMOR CELLS.

Nelson DJ, Kiremidjian-Schumacher L, Stotzky G
Sloan-Kettering Inst., Rye, NY, 10580
Environ Res; 28(1):154-163 1982

Cadmium at 10(-5) and 10(-6) M significantly inhibited the ability of immune macrophages from C57BL/6J mice to destroy Sarcoma I cells. These concentrations of cadmium apparently interfered with the cytolytic mechanism(s) of macrophages, and the inhibition did not result from toxicity of the metal toward either cell type. (Author abstract) (48 Refs)

82. ACTIVATED MACROPHAGE MEDIATED CYTOTOXICITY FOR TRANSFORMED TARGET CELLS.

Hibbs JB, Grnager DL, Cook JL, Lewis AM, Clark W, Hanna M, Berke G, Nathan C
Dept. Medicine, Div. Infectious Diseases, Univ. Utah Sch. Medicine, Salt Lake City, UT, 84148
Adv Exp Med Biol; 146(82):315-332 1982

Inhibition of metabolic pathways in the nucleus of transformed target cells caused by cytotoxic activated macrophages (CAMP), evidence that CAMP cause perturbation of energy homeostasis in murine L1210 leukemia cells, existence of at least two transformed cell phenotypic responses to CAMP, and evidence that the nonlytic transformed cell phenotype may be a marker for increased tumorigenic virulence are discussed. The highly reproducible pattern of metabolic inhibition induced in transformed target cells by CAMP is possibly similar to the yet undefined pattern of metabolic inhibition that may occur in certain types of programmed cell destruction during normal growth and development. (28 Refs)

83. CONTRIBUTION TO MORPHOLOGY OF MALIGNANT HISTIOCYTOSIS.

Rudiger KD, Schreiber D
Institut fur Allgemeine Pathologie und Pathologische Anatomie, Medizinischen Akademie, DDR-5060 Erfurt, Nordhauser Strasse 74, E. Germany
Zentralbl Allg Pathol; 126(1/2):133-141 1982

Nine cases of malignant histiocytosis (3 males, 6 females, age 30 to 83 years) have been observed in the biopsy and autopsy material of the Institute of General Pathology and Pathological Anatomy of the Medical Academy of Erfurt, GDR. Malignant histiocytosis which derives from tissue macrophages/histiocytes is characterized by a proliferation of non-cohesive atypical histiocytes mainly in lymph nodes, spleen, liver, and bone marrow. The tumor cells are large, pleomorphic and show an irregularly-shaped, cleaved and often kidney-like nucleus with 1-3 medium-sized nucleoli. The cytoplasm is moderately basophilic and grey-blue when stained with azure B eosin or according to Pappenheim. Diffuse cytoplasmic activities of nonspecific esterase and acid phosphatase are further properties. Another sign of malignant histocytic cells should be stressed, ie, the diffuse intracytoplasmic perinuclear PAS-positive spot which hitherto has not been mentioned in the literature. Morphological variants of malignant histiocytosis are fibrosing (2 cases) and erythrophagocytosing types (2 cases). Reactive histiocytoses, histiocytosis X and malignant non Hodgkin-lymphomas, esp immunoblastic lymphomas, are to be taken into account in differential diagnosis. (Author abstract) (33 Refs) (In GER)

84. BOVINE MONOCYTE-INDUCED TUMOR CELL CYTOTOXICOSIS.

Atluru D, Johnson DW
Dept. Large Animal Clinical Sciences, Coll. Veterinary Medicine, Univ. Minnesota, St. Paul, MN, 55108
Am J Vet Res; 43(6):989-991 1982

Human monocytes have been shown to be highly cytotoxic for tumor cells in vitro. To determine whether these observations could be extended to the bovine species, monocyte-induced tumor cell cytotoxicosis was examined in vitro. Target cells were initiated from benign hyperplastic corneal plaque lesions or ocular squamous cell carcinoma lesions in cattle. The monocyte-induced tumor cell cytotoxicosis, as measured by target cell [3H]thymidine incorporation, was highly significant (p less than 0.001) in corneal plaque cells at target:effector cell ratios of 1:10, 1:5, and 1:1. The [3H]thymidine incorporation was also highly significant (p less than 0.001) in squamous cell carcinoma cells at target:effector cell ratios of 1:10 and 1:5, but of less significance (p less than 0.01) at 1:1. Further, the ability of bovine monocytes to kill target cells was enhanced by culturing effector cells for 3 days before assay. These data show that bovine monocytes are cytotoxic for tumor cells in vitro and indicated that bovine monocytes may be of importance in the control of neoplastic proliferation in vivo. (Author abstract) (15 Refs)

85. DISSOCIATION BETWEEN TUMOUR CELL CYTOSTATIC AND IMMUNO-SUPPRESSIVE CAPACITY OF HUMAN MONOCYTES ACTIVATED WITH LYMPHOKINES.

Unsgaard G, Hammerstrom J, Lamvik J
Trondheim Regional Hosp., N-7000 Trondheim, Norway
Acta Pathol Microbiol Scand [C]; 90(2):73-79 1982

Activation of monocytes with lymphokines from BCG-stimulated lymphocytes increased the capacity to inhibit DNA-synthesis in a tumor cell line (NHIK 3025) at all stages of monocyte maturation in vitro. However, the capacity of monocytes to suppress DNA-synthesis in mixed lymphocyte cultures (MLC) was reduced, indicating a dissociation of the immunosuppressive and tumor cell cytostatic functions of lymphokine-activated monocytes. Supernatants of lymphokine-activated monocytes inhibited DNA synthesis in the tumor cell line, but not in MLC. Monocytes from donors with a strong tuberculin reaction produced supernatants with a stronger cytostatic activity than monocytes from donors with a weak tuberculin reaction. By in vitro maturation, even the latter monocytes acquired ability to produce supernatants that were strongly inhibitory to tumor cells. (Author abstract) (23 Refs)

86. GROWTH FACTORS IN HODGKIN'S DISEASE.

Ford RJ, Mehta S, Davis F, Maizel AL
Dept. Anatomic Pathology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77025
Cancer Treat Rep; 66(4):633-638 1982

Tumor nodules from spleens removed at staging laparotomy for nodular sclerosing Hodgkin's disease were grown as fragment cultures in vitro. These cultures could be maintained in vitro for up to 2 months and consisted of 90% large, adherent multinuclear and mononuclear cells. Immunologic markers and enzyme histochemistry suggested that the cultured cells belonged to the monocyte/macrophage lineage. Supernatants from these cell cultures were then assayed for the monokine Interleukin 1 and for fibroblast stimulatory factors, which were both present. These results are discussed in considering Hodgkin's disease as a neoplasm of the monocyte/macrophage lineage, capable of producing functionally active mediators that may account for the histopathologic appearance observed. (Author abstract) (20 Refs)

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY

87. INHIBITION OF ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC) BY NORMAL AND PATHOLOGICAL SERA FROM PATIENTS WITH ADVANCED LUNG CANCER.

Fekete B, Sachno L, Tamassy K, Pal A, Angyal I, Forrai I
Natl. Koranyi Inst. for Tuberculosis and Pulmonology, Piheno ut 1, H-1529 Budapest, Hungary
Haematologia (Budap); 14(4):417-423 1981

Technical variables interfering with the detection of Fc-receptor blocking activity of tumor sera were studied using sera from 37 lung cancer patients and 40 normal donors. Washing of effector cells preincubated with pathological sera did not affect the level of inhibition of antibody-dependent cellular cytotoxicity (ADCC). The ADCC inhibition test proved to be reproducible both with and without preincubation and washing. The inhibition of ADCC by sera was not attributable to a direct cytotoxic effect since no difference in viability of target cells treated with human serum albumin, mixed AB serum, or inhibitory sera was observed by trypan blue exclusion. Inhibitory activities of normal and tumor sera were measured in two lymphocyte donors. Serum concentration affected the degree of inhibition, but an increase in the efficacy of inhibition attributed to an increase in concentration was statistically linear only in certain combinations. The difference between tumor and control sera was statistically highly significant in all the experiments. When analyzing the percentage inhibition of ADCC produced by sera, functions able to discriminate between normal and tumor sera could be established. Data presented showed that discriminatory ability of the functions was optimum at serum concentration of 4% for Donor 2 and at 20% for Donor 1. Results indicated that both normal and tumor sera from patients with advanced lung cancer contain blocking factors which may be responsible for the impairment of ADCC activity, but the levels of inhibition exerted by tumor sera are significantly higher than those of normal sera. (21 Refs)

88. IDENTITY OF EFFECTOR CELLS PARTICIPATING IN THE REVERSE ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY.

Saxena RK, Saxena QB, Adler WH
Natl. Inst. Aging, NIH, 4940 Eastern Ave., Baltimore, MD, 21224
Immunology; 46(2):459-464 1982

Our previous work has shown that antibody-coated mouse spleen cells express enhanced cytotoxic activity against some Fc-receptor-bearing target tumor cells by a mechanism which appears to be similar to an antibody-dependent cell-mediated cytotoxicity (ADCC) reaction with reversed polarity of the antibody bridge (R-ADCC). In this report we have shown that (i) the levels of basal natural killer (NK), ADCC and R-ADCC cytotoxic activities in mouse spleen cells are strongly correlated with each other, (b) simultaneous induction of ADCC and R-ADCC reactions does not result in an additive cytotoxic response, and (iii) YAC cells which do not bear Fc receptors and are highly sensitive to lysis by NK can specifically and competitively inhibit the ADCC and R-ADCC reactions. These results suggest that the R-ADCC reaction may be mediated by the same effector cell population as mediates NK and ADCC reactions against tumor target cells. (Author abstract) (10 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

89. MECHANISM OF T CELL-MEDIATED CYTOLYSIS: AN INVESTIGATION OF CELLS AND STAGES AFFECTED BY CYTOLYSIS-INHIBITING MONOCLONAL ANTIBODIES.

Hayot B, Pierres M, Golstein P
Centre d'Immunologie INSERM-CNRS de Marseille-Luminy Case 906, 13288 Marseille Cedex 9, France
Adv Exp Med Biol; 146(82):469-485 1982

Two essential points for assessment of the potential usefulness of monoclonal antibodies (MAB) are discussed: inhibition of cytolysis by interaction of MAB with the effector or the target cells and stage of the cytolytic process on which MAB were acting. None of MAB acted at the last stage; methodological limitations prevented the identification of whether the inhibition was at recognition and/or lethal hit. Six xenogeneic rat antimouse MAB were selected for their inhibitory effect on T cell-mediated cytolysis; 17.2 MAB was very probably directed against Lyt-2. (22 Refs)

90. A NEW ACUTE LEUKEMIA-ASSOCIATED BLAST CELL ANTIGEN DETECTED BY A MONOCLONAL ANTIBODY.

Billing R, Lucero K, Shi BJ, Terasaki PI
Tissue Typing Lab., Dept. Surgery, Univ. California Los Angeles, 1000 Veteran Ave., Room 15-22, Los Angeles, CA, 90024
Blood; 59(6):1203-1206 1982

A monoclonal mouse antibody has been raised to the common acute lymphoblastic leukemia (cALL) cell line Reh. It is a cytotoxic antibody of the IgG2a subclass that reacts with leukemia cells from the following patients: 69% non-B non-T ALL, 50% T-ALL, 18% acute myeloblastic leukemia (AML), and 66% chronic myeloid leukemia (CML) blast crisis lymphoid cells. Other types of leukemia and all normal blood cells tested were negative, including T and B lymphocytes, granulocytes, monocytes, erythrocytes, and spleen cells. The detected antigen appears to be a type of blast cell antigen because it is also present on phytohemagglutinin (PHA) blast cells, myeloblast from normal bone marrow cells (by CFU-C), and all lymphoblastoid cell lines tested. Only one active antibody species could be detected by preparative isoelectric focusing on polyacrylamide gels and by protein-A-Sepharose affinity chromatography. (Author abstract) (17 Refs)

91. HUMAN BLOOD LYMPHOCYTE SUBSETS SEPARATED ON THE BASIS OF NYLON ADHERENCE, SRBC AND EA ROSETTING: NATURAL CYTOTOXICITY AND CHARACTERIZATION WITH MONOCLONAL REAGENTS.

Masucci G, Masucci MG, Klein E
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Cell Immunol; 69(1):166-174 1982

Lymphocyte subsets were separated by nylon-wool adherence, E-rosetting, and presence of Fc-gamma receptor (as defined by EA-rosetting capacity), and characterized by reactivity with the following monoclonal antibodies: OKT3, OKT4, OKT8 (reactive with T lymphocytes and T-lymphocyte subsets). OKM1 (reactive with cells of myelomonocytic origin), and OKIa-1 (reactive with HLA-Dr antigens). The majority of the OKM1-positive cells were collected in the EA+ compartment of the E-, and low-avidity E+ subpopulations. In spite of the separation as E rosettes, the EA+ low-avidity E+ cells did not react with OKT3 and OKT4. However, a proportion of these cells reacted with OKT8. these cells had high anti-K562 cytotoxicity. the EA-receptor-negative part of the E- subset, which had less OKM1-positive cells, was also active against K562. Activated T cells may have contributed to the activity of this fraction, because OKT3-and OKIa-1 positive cells were present. When Daudi was used as target, only the EA-rosette-negative parts of the E- and low-avidity E+ subsets were lytic. This activity was more evident after IFN activation of the effector lymphocytes. After introduction of the markers defined by monoclonal antibodies the heterogeneity of the NK-active population was still a fact. At least three cell types defined by these reagents were enriched in the different cytotoxic fractions: OKM1-, OKT8-, and OKIa-1-positive cells. The fact that part of NK activity was exerted by cells separated on the basis of SRBC rosetting and in the SRBC rosette-negative subsets, a high proportion of the cells reacted with monoclonals, which define T markers, confirms previous suggestions that the majority of NK cells belong to the T lineage. (Author abstract) (27 Refs)

92. REACTION SPECIFICITY OF MONOCLONAL ANTIBODY MADE BY CELL FUSION.

Shimoyama M, Tobiuch K, Hirose M, Minato K
Dept. Internal Medicine, National Cancer Center Hosp., Tokyo, Japn
Nippon Rinsho; 39(8):2780-2789 1981

Numerous monoclonal antibodies that specifically react with the differentiation antigen of T cells have been isolated. Those that react to pan T-cells specifically bind polypeptides of molecular weight 65,00-70,000, and those that react to below 10% of thymus cells bind to a peptide with mol wt 19,000. Those that react to E-rosette formation receptors specifically bind polypeptides of mol wt 40,000-50,000. Those binding human Thy-1 antigen and those that react only to thymus T-cells are also known. Two subsets of peripheral T cells, inducer/helper T (T I/H) and suppressor/cytotoxic T (Ts/c) are known, and monoclonal antibodies specifically react to these two T cells are also available. No cross reaction between T I/H and Ts/c in peripheral T cells was found; however, 70-80% cross reaction are observed in thymus cells (mainly cortical thymocyte). Using the reaction of OKT monoclonal antibody series, a clear relationship of differentiation and maturation process of thymus T cells to the two subsets, T I/H and Ts/c of the peripheral T cells has been established. This relationship will be extremely useful for the analysis of T cell type tumor cells. Unlike those against T cells, relatively limited numbers of monoclonal antibodies against B-cell angens, lymphocytic stem cell antigens, and myelocytic cell antigens are available. Reaction of monoclonal antibodies against 25 tissue culture cell lines derived from hematopoietic cell tumors is highly specific, and is used to determine the differentiation degree of each tissue culture. Monoclonal antibody is extremely useful for determination of the tumor cell source or the maturity of normal cells. (57 Refs) (In JPN)

93. ALTERATIONS IN THE PHENOTYPE OF HAIRY CELLS DURING CULTURE IN THE PRESENCE OF PHA: REQUIREMENT FOR T CELLS.

Worman CP, Beverley PC, Cawley JC
Dept. Haematology, Univ. Coll. Hosp., Grafton Way, London WC1, England
Blood; 59(5):895-899 1982

Culture studies of peripheral blood mononuclear cells from seven entirely typical cases of hairy cell leukemia showed that after culture in the presence of PHA for 2-5 days, the predominant cell type changed from E- SIg+ CIg+ gammaFcR+ muFcR+ hairy cells to an E+ SIg- CIg- gammaFcR- muFcR- population of transformed cells derived from hairy cells. Depletion and readdition experiments demonstrated that cell-to-cell contact with T cells was necessary for the phenotypic change, while several observations indicated that the E+ population was not derived from T cells present before culture. The E positivity of the cultured cells was shown to be due to the possession of E receptor not acquired from the culture fluid, but the cells differed from true T cells in lacking both mature and immature T-cell antigens. The relevance of these in vitro observations to the continuing controversy concerning the nature of the hairy cells and to the in vivo fluctuations in immunologic phenotype not infrequently observed in hairy cell leukemia is briefly discussed. (Author abstract) (23 Refs)

94. HUMAN NEUTROPHIL FCGAMMA RECEPTOR DISTRIBUTION AND STRUCTURE.

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Dept. Cellular Physiology and Immunology, Rockefeller Univ., New York, NY, 10021

Proc Natl Acad Sci USA; 79(10,part1):3275-3279 1982

Fc receptors (FcR) for IgG on human cells were analyzed with two monoclonal antibodies, 3G8 and 4F7. Fab fragments of both hybridoma IgGs inhibited binding to neutrophils of soluble rabbit IgG complexes and sheep erythrocytes (E) coated with rabbit IgG. The number of sites for 3G8 Fab was 135,000 per neutrophil, roughly equivalent to the number of sites for rabbit IgG in immune complexes (112,000 per cell). We did not observe human IgG1 binding sites on neutrophils, although binding of IgG1 to FcR-bearing lines U937 and HL-60 was readily demonstrated. Other cell types bearing 3G8 binding sites were mature chronic myelogenous leukemia cells, eosinophils, 6% of E-rosetting lymphocytes, and 15% of Ig-bearing peripheral lymphocytes. No binding of 3G8 Fab was observed on the FcR-bearing cell lines U937, HL-60, Raji, Daudi, and K562 or on blood monocytes. However, 15% of monocytes cultured for 7 days and 60% of lung macrophages expressed 3G8 antigen. When analyzed by sodium dodecyl sulfate/polyacrylamide gel electrophoresis, the neutrophil FcR immunoprecipitated with 3G8 or 4F7 Fab-Sepharose displayed a broad band extending from Mr 73,000 to 51,000; in many experiments this band was resolved into two poorly separated components, centered at Mr 66,000 and 53,000. These results show that human neutrophil FcR for IgG is different from that on monocytes, with respect to both antigenic composition and binding of monomeric IgG1. (Author abstract) (35 Refs)

95. NATURALLY OCCURRING CELL-MEDIATED CYTOTOXICITY: AN IN VITRO PHENOMENON DISTINCT FROM THE ANTIBODY-DEPENDENT CELLULAR CYTOTOXIC REACTION (MEETING ABSTRACT)

Banerjee D, Richter MA

Department of Pathology, University of Western Ontario, Ontario, Canada

Lab Invest; 46(1):93A 1982

Normal circulating human leukocytes consistently lyse rabbit erythrocytes within 24 hours in culture. The effector cell is a C3/Fc receptor-bearing cell with phagocytic properties since specific depletion of C3 receptor-positive, Fc receptor-positive, or phagocytic, cells results in a marked decrease in cytotoxic activity. Unlike the antibody-dependent cellular cytotoxic (ADCC) reaction, the cytotoxic reaction in this system (NOCC) requires no specific antitarget cell antibody, cannot be inhibited by the blocking of Fc receptors by heat-aggregated gamma-globulin, and is inhibited by fetal bovine serum and by trypsin treatment of the effector cells. The NOCC cytotoxic reaction is dependent upon direct effector-target contact and is not mediated by soluble substances, nor is it mediated through a phagocytic process. (no Refs)

96. CARBOHYDRATE DIFFERENCES IN HUMAN HIGH MOLECULAR WEIGHT ANTIGENS OF B- AND T-CELL LINES.

Morishima Y, Ogata S, Collins NH, Dupont B, Lloyd KO
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Immunogenetics; 15(5):529-535 1982

High mol-wt glycoproteins of human hematopoietic cells were analyzed using a new mouse monoclonal antibody (moAb 4C). Serological analysis using indirect immunofluorescence and absorption studies demonstrated that the antigen (Leu 200) detected by moAb 4C is restricted to hematopoietic tissue and is expressed on all peripheral lymphocytes, monocytes, granulocytes, a majority of thymocytes, spleen cells, and bone marrow cells. The carbohydrate moieties of Leu 200 glycoproteins were also described. (21 Refs)

97. IMMUNOGENIC VARIANTS OBTAINED BY MUTAGENESIS OF MOUSE MASTOCYTOMA P815: III. CLONAL ANALYSIS OF THE SYNGENEIC CYTOLYTIC T LYMPHOCYTE RESPONSE.

Maryanski JL, Van Snick J, Cerottini JC, Boon T
Ludwig Inst. Cancer Res., UCL 7459 Avenue Hippocrate, B-1200 Brussels, Belgium
Eur J Immunol; 12(5):401-406 1982

The cytolytic T lymphocyte (CTL) response of syngeneic mice to antigenic variants obtained by mutagenesis of mastocytoma P815 was analyzed at the clonal level. Estimates of the frequency of CTL precursor cells in spleens from mice immunized with P815 variants ranged from 10(-4) to 2 x 10(-3). This frequency could be increased approximately 100x by stimulating immune spleen cells in mass culture for 6-8 days with the immunizing variant. Specificity analysis of a large number of individual CTL clones demonstrated the existence of two distinct populations of CTL. Some CTL clones lysed exclusively the immunizing variant, while others lysed equally well all P815 targets, but not syngeneic tumor L1210. These results provide direct evidence for the existence of new, individual specificities on P815 variants in addition to a common antigen already present on the original P815 cells. This confirms that a variety of new antigens can be induced by mutagenesis on the same background cells. Stable, highly active CTL clones specific for either individual variant antigens or common P815 antigens could be maintained in long-term culture. (Author abstract) (26 Refs)

98. A B LYMPHOMA CELL LINE PRODUCES GROWTH FACTORS FOR HEMOPOIETIC, LYMPHOID, AND MAST CELLS.

Clark-Lewis I, Schrader JW, Wu YY, Harris AW
Walter and Eliza Hall Inst. Medical Res., Royal Melbourne Hosp., Post Office, Victoria 3050, Australia
Cell Immunol; 69(1):196-200 1982

A cloned B lymphoma cell line (WEHI-231.1) released P-cell stimulating factor, a factor allowing the in vitro growth of presumptive mast cell precursors together with small amounts of T-cell growth factor and granulocyte-macrophage colony-stimulating factor. These factors were produced without deliberate stimulation of the B lymphoma cells. Lipopolysaccharide-stimulated nude mouse spleen cells also released low levels of P-cell stimulating factor and granulocyte-macrophage colony-stimulating factor. These results raise the possibility that B cells may produce regulatory factors. (Author abstract) (20 Refs)

99. INCREASED RATE OF REPAIR OF ULTRAVIOLET-INDUCED DNA STRAND BREAKS IN MITOGEN STIMULATED LYMPHOCYTES.

Hamlet SM, Lavin MF, Jennings PA
Dept. Biochemistry, Veterinary Pathology, and Public Health, Univ. Queensland, Brisbane, 4067, Queensland, Australia
Int J Radiat Biol; 41(5):483-491 1982

Previous results from this laboratory have shown that phytohemagglutinin-stimulated bovine lymphocytes exhibit a peak of ultraviolet-induced DNA repair synthesis 3 to 4 days after addition of mitogen. The level of repair synthesis was approx 10 fold higher than that in unstimulated lymphocytes. We have extended these studies to examine the rate of repair of strand breaks in UV-irradiated bovine lymphocytes. The extent of breakage of DNA was shown to be the same in mitogen-stimulated and unstimulated lymphocytes from two breeds of cattle, when determined by sedimentation of nucleoids on sucrose gradients. However, in mitogen-stimulated cells the time taken to repair DNA strand breaks was 6 hours compared to 12 hours in stationary phase lymphocytes after a UV dose of 5 J/m2. These results suggest that the increased rate of repair of strand breaks is due to the induction of enzymes involved at the post-incision stage of DNA repair. Thus the increased level of repair synthesis observed in earlier work correlates with an increased rate of repair of DNA strand breaks in phytohemagglutinin-stimulated bovine lymphocytes. (Author abstract) (20 Refs)

100. LOW DOSE RADIOSENSITIVITY OF ALLOIMMUNE CYTOTOXIC T CELLS.

Spellman C, Anderson RE
Dept. Pathology, Univ. New Mexico, Sch. Medicine, Albuquerque, NM, 87131
J Exp Med; 155(6):1858-1863 1982

The radiosensitivity of cells which express cytotoxic effector activity with particular emphasis on low dose x-rays (10-25 rad) was investigated, and the Lyt phenotype and proportion of radiosensitive cells susceptible to interphase death were determined. Spleen lymphocytes from female C57BL/6 B10, B10.A, BALB/c, BALB/c-H-2k, CBA, SJL, and DBA/2 mice were used. Cytotoxic response was determined in a short-term 51Cr release assay. When groups of mice were tested at radiation doses of 1, 10, 25, 50, 100, or 200 rad, a distinct and precipitous drop in the number of lytic cells was observed after exposure to 10-25 rad. Cells resistant to high dose irradiation were also present. All strains tested exhibited radiosensitive and radioresistant cytotoxic T lymphocytes (CTL). Variation in the radiosensitive CTL populations different responder strains was not dependent upon the efficiency of allosensitization. Radiosensitive CTL were a general component of cytotoxic allogeneic responses. Generation of radiosensitive CTL effector cells was most pronounced in animals with the C57BL background. The mechanism of low dose radiosensitivity appeared to be interphase death. (11 Refs)

101. E RECEPTOR EXPRESSION OF T LYMPHOCYTES IN T LYMPHOPROLIFERATIVE DISEASES.

Jonsson V, Andersen BL, Brandrup F, Christensen BE, Rothenborg HW, Thomsen K
Medical Dept. C., Hematology Lab., Gentofte Univ. Hosp., 2900 Hellerup/Copenhagen, Denmark
Scand J Haematol; 28(4):329-334 1982

The lymphoid component of skin infiltrates from six cases of mycosis fungoides and two cases of T cell chronic lymphatic leukemia consisted almost exclusively of T lymphocytes with abnormally high E receptor expression. Such T cells were also found to dominate the skin infiltrates from 10 patients with severe atopic dermatitis. Blood T lymphocyte counts from all types of patients were within the normal range, but even the blood T lymphocytes of the patients had a strong E receptor expression. The bone marrow in atopic dermatitis and in mycosis fungoides showed normal T cell counts with normal E receptor expression. Supported by basic lymphocyte-kinetic considerations it is likely that the skin in T lymphoproliferative diseases is characterized by an abnormal ability to home and/or to trap T lymphocytes with strong E receptor expression. (Author abstract) (22 Refs)

102. T-CELL SUBPOPULATIONS IDENTIFIED BY MONOCLONAL ANTIBODIES AFTER HUMAN MARROW TRANSPLANTATION. I. HELPER-INDUCER AND CYTOTOXIC-SUPPRESSOR SUBSETS.

Atkinson K, Hansen JA, Storb R, Goehle S, Goldstein G, Thomas ED
Dept. Haematology, St. Vincent's Hosp., Darlinghurst, Sydney, NSW 2010, Australia
Blood; 59(6):1292-1298 1982

Peripheral blood helper-inducer and cytotoxic-suppressor T-cell subpopulations in patients receiving marrow transplants for the treatment of acute leukemia or severe aplastic anemia were quantitated on the fluorescence-activated cell sorter (FACS) using the monoclonal antibodies OKT4 and OKT8, respectively. The relative (percent) and absolute number of OKT4+ cells were severely and persistently depleted for up to 2.7 yr posttransplant. In contrast, the percent and absolute number of OKT8+ cells began to recover within the first 60 days of transplant and subsequently remained at normal or high levels for periods of up to 7.3 yr. There was no significant difference in percent or absolute numbers of OKT8+ cells for patients with or without acute graft-vs-host disease (GVHD). The reversal of the normal OKT4:OKT8 ratio (2:1) occurred regardless of whether the recipient was given an allogeneic, syngeneic, or autologous transplant and regardless of whether or not acute or chronic GVHD developed. The reversed ratio was due in the first 3 mo posttransplant to low numbers of OKT4+ cells and later to a combination of low numbers of OKT4+ and high numbers of OKT8+ cells. Normalization and then an increase in the number of OKT8+ cells correlated with increasing time posttransplant and not with resolution of acute GVHD. (Author abstract) (21 Refs)

103. INDUCTION OF IN VITRO PROLIFERATION AND MATURATION OF HUMAN ANEUPLOID MYELOGENOUS LEUKEMIC CELLS.

Chiao JW, Andreeff M, Freitag WB, Arlin Z
Sloan-Kettering Inst. Cancer Res., New York, NY, 10021
J Exp Med; 155(5):1357-1369 1982

Terminal maturation of aneuploid leukemic cells from patients with acute myelogenous leukemia was induced by supplementation of media with lymphocyte-conditioned medium (CM). Cells in culture suspensions underwent changes in morphology, and some cell aggregates were detected. As the proportion of monocyte- and macrophage-like cells increased with time, the proportion of immature cells decreased. Flow cytometric measurement of cells during the maturation-induction period showed an appearance of cell populations having lower cellular RNA content than populations not treated with conditioned medium. CM-induced maturation of leukemic cells to monocyte- and macrophage-like cells appears to be independent of DNA abnormality. In three patients studied, hyperdiploid DNA stem lines were found in all cells throughout the culture period. Macrophage-like cells with mature functional and marker features had the same aneuploid stem line as the undifferentiated cells, establishing the leukemic origin of the differentiated cells. Because of the higher rate of proliferation in the CM-supplemented cultures than in those lacking CM, interaction of CM with cells seems to have resulted in stimulation of some cells from the resting to the replicating phase. (22 Refs)

104. TWO ANTI-TUMOR CYTOTOXIC CELLS IN THE PERITONEAL CAVITY OF RATS: NATURAL OCCURRENCE, AUGMENTATION AND PARTIAL CHARACTERIZATION.

Inoue Y, Nelson DS
Kolling Inst. Medical Res., Royal North Shore Hosp. Sydney, Sydney, St. Leonards, NSW 2065, Australia
Aust J Exp Biol Med Sci; 60(1):41-53 1982

Mononuclear cells cytotoxic to methylcholanthrene-induced fibrosarcoma cells were detected in the peritoneal cavities of normal rats by means of 16 hr 51Cr release and 48 hr 125IUdR release assays. Carriage of a tumor which induces concomitant immunity, or intraperitoneal injections of Corynebacterium parvum or proteose-peptone, led to increases in mononuclear cell numbers. Injections of C parvum and protease-peptone led to increases in cytotoxicity in 51Cr release assays. Carriage of an immunogenic tumor led to an increase in cytotoxicity to homologous tumor cells in the 125IUdR release assay. Cells were separated by sedimentation velocity, metrizamide density gradients and adherence to glass or plastic. Small cells were more active than large cells in 51Cr release assays. Larger cells tended to be more active in 125IUdR release assays. Larger cells tended to be more active in 125IUdR release assays. Generally, low density cells were more active in both assays, except that high density cells induced by C parvum were more active in 125IUdR release. Adherent cells from C parvum-injected rats were more active than non-adherent cells in both assays. On the basis of differential stimulation and separation by sedimentation velocity it is suggested that two cell types, possibly NK cells and macrophages, are operative. 125IUdR-labeled fibrosarcoma cells were lysed after intraperitoneal injection into normal and concomitantly immune rats, more rapidly and extensively in the latter case. The cytotoxic cells may be important in both natural and acquired resistance of rats to tumor growth. (Author abstract) (31 Refs)

105. SPECIFICITY OF NATURAL KILLER (NK)-CELL ACTIVITY AGAINST TARGET CELLS DERIVED FROM CARCINOMA OF THE PROSTATE (MEETING ABSTRACT)

Schmitz-Drager BJ, Ackermann R, Heckl W
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Earlier experiments have demonstrated that NK-cells, a distinct subpopulation of peripheral mononuclear cells (PMC), are responsible for the killing of various tumor cells in vitro. Further knowledge of the yet unknown specificity of these reactions is needed to understand the role of NK-cells in the defense of malignant tumors. This study was designed to investigate the specificity of NK-cell reactions in carcinoma of the prostate (CaP). Cell lines DU 145, PC 3, PC 93 and EB 33 derived from CaP were used as absorption monolayers and target cells in checkerboard experiments. HeLa cells and cell line K 562 known for its high NK-cell susceptibility served as control. Spntaneous cell-mediated cytotoxicity (SCMC) of PMC from healthy donors was determined in a 4 hour 51 Cr release assay. The results indicate that all cell lines exhibit target structures which are recognized by the same subset of NK-cells. However after complete absorption on monolayers of a given cell line residual SCMC was still detectable against K 562 residual SCMC was still detectable against K 562 target cells. This residual SCMC could be removed by cold inhibition with unlabeled K 562 target cells but not with target cells of any other cell line. (no Refs)

106. CHARACTERIZATION OF HAMSTER NK CELLS (MEETING ABSTRACT)

Teale DM, Rees RC, Clark A, Potter CW

Department f Virology, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, England

Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

The importance of NK (natural killer) cells in tumor immunology has previously been reviewed, and their association with large granular lymphocytes has been described in the human, rat and mouse. In this report we describe the existence of a cytotoxic cell population, in hamster peripheral blood, capable of lysing NK susceptible target cells in a 4-hr Chromium-release assay. These cells proved to be nonadherent to nylon wool, non-phagocytic and capable of lysing xenogeneic targets. When separated on Percoll Discontinuous Density Gradients cytotoxicity was associated with fractions enriched for large, sometimes granular, lymphocytes. In addition, cells with morphology of large lymphocytes were shown to bind to NK sensitive target cells. NK activity was only demonstrable in spleen and peripheral blood, with low levels in peritoneal exudate cells, and activity was shown not to be age-restricted. (4 Refs)

107. POSSIBLE ORIGIN OF THE REED-STERNBERG CELL FROM AN INTERDIGITATING RETICULUM CELL.

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Cancer Treat Rep; 66(4):601-608 1982

In a comparative immunologic and cytochemical analysis, Reed-Sternberg (RS) cells from seven patients with Hodgkin's disease were found to more closely resemble interdigitating reticulum cells (IDC) than normal or malignant histiocytic reticulum cells (macrophages); malignant macrophages were established as a cell line from a patient with malignant histiocytosis. RS cells and IDC both showed strong expression of human Ia-like antigens, a close physical association with helper/inducer T cells, and a lack of at least two common macrophage antigens. Supportive evidence of the identity of RS cells and IDC was their lack of lymphoid and myeloid characteristics, smaller content of nonspecific esterase and acid phosphatase than that in histiocytes, similar cytology, and location in thymic-dependent regions of lymphoid tissues. Malignant transformation of the IDC to an RS cell could result in diminished antigen-presenting capacity and contribute to the defect in T-cell-mediated immunity that commonly occurs in Hodgkin's disease. (Author abstract) (27 Refs)

CMI METHODOLOGY

108. DETECTION OF CARCINOGENIC EXPOSURES BY URINALYSIS: INDUCTION OF CELL-MEDIATED IMMUNITY.

Stevens RH, Cole DA

Radiation Res. Lab., Dept. Radiology, Univ. Iowa, Iowa City, IA, 52242

Toxicol Lett; 11(3/4):299-303 1982

The colon carcinogen 1,2,-dimethylhydrazine (DMH: 0.1 to greater than 10 mg/kg) was administered sc to male Fisher F344 inbred rats; urine was collected over a 24 hr period and injected ip into a group of normal unexposed rats. DMH and its metabolites were excreted within 15 min in the urine and nearly 65% metabolized over a 24-hr interval. Cell mediated immunity (CMI) was measured by killing/injury of cultured x-ray induced rat small bowel adenocarcinoma target cells by peripheral blood lymphoid cells of urine-exposed animals. CMI was increased by urine collected from DMH exposed rats; a dose-response curve relationship was found, suggesting the presence of mutagenic/carcinogenic components. Although the actual DMH concentration in the urine was not known, it was less than 10(-4) times LD50 (1 g/kg) and 10(-3) times the amount necessary for tumor induction over a 20-mo latency period. This method has potential as a rapid non-invasive technique for screening individuals exposed to carcinogens. (15 Refs)

109. CLINICAL APPLICATION OF A WHOLE BLOOD ASSAY FOR DETERMINATION OF NATURAL CYTOTOXICITY (MEETING ABSTRACT)

Morales A, Ottenhof PC

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Current methods for assessment of natural killer (NK) activity expose the effector cells to a series of preparatory washes which are time consuming and, frequently detrimental and inefficient in terms of cell recovery. These procedures also alter and bias the concentration of NK cells and other blood elements. We have recently described a method for assessment of NK activity utilizing unseparated, whole blood. The assay is easy to perform, quick and eminently suitable for screening and monitoring of natural cytotoxicity. A normative study has been conducted to assess the clinical usefulness of the assay. More than 80 normal subjects and over 50 patients with tumors of the urinary tract have been investigated. Relevant observations from the study include: a) the whole blood assay is more reliable than currently available techniques and a truer reflection of in vivo events; b) among normal individuals there are 2 clearly defined responder populations: one of high and one of low reactors; the significance of this finding remains to be determined; c) there is a significant difference in reactivity between normal individuals and patients with localized neoplasms of the urinary tract; d) there is also a significant difference between patients with localized tumors and those with metastatic disease; e) the assay is useful in the immunological assessment of cancer patients and in monitoring the course of their disease and response to treatment; f) non-specific immunotherapy induces significant changes in NK activity which are readily demonstrated with this assay. (1 Ref)

110. MOUSE RED CELL ROSETTE FORMATION AND THE COLCHICINE SENSITIVITY TEST: RELATIVE USEFULNESS IN THE DIFFERENTIAL DIAGNOSIS OF CHRONIC LYMPHOCYTIC LEUKAEMIA AND B LYMPHOCYTIC LYMPHOMA.

Sugden PJ, Lilleyman JS
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J Clin Pathol; 35(4):376-379 1982

Mouse erythrocyte (M) rosette formation and colchicine sensitivity were compared for their ability to differentiate chronic lymphocytic leukemia (CLL) from B cell non-Hodgkin's lymphoma (NHL) with overspill. Twenty-two cases of CLL and 8 of NHL were studied along with 31 normal adults. Results from the patients in both tests differed significantly from the controls but colchicine sensitivity failed to differentiate them further. M rosettes, on the other hand, while increased in some patients with NHL were, without overlap, much more numerous in those with CLL, and clearly distinguished the two conditions. A significant autolymphocytotoxic effect of plasma from both study groups was also noted which was not found in the controls. (Author abstract) (12 Refs)

111. IDENTIFICATION OF CARCINOGENS BY MEASUREMENT OF CELL-MEDIATED IMMUNITY: II. ASSAY SPECIFICITY.

Stevens RH, Cole DA
Dept. Radiology, Radiation Res. Lab., Univ. Iowa, Iowa City, IA, 52242
Environ Res; 28(1):67-76 1982

Studies utilizing the Fischer F334 inbred rat model were undertaken to define the specificity for antitumor cell-mediated immune (CMI) measurements as determined by lymphoid-cell cytotoxicity to determine whether such values could serve as an analytical reflection for the carcinogenic potential of environmental pollutants. The investigations revealed that specificity was apparently limited to a carcinogenic insult and designated by the embryonic origin of the affected tissue. For example, it was found that animals having x-ray-induced small-bowel, 1,2-dimethylhydrazine-induced colon, and 7,12-dimethylbenz[a]anthracene-induced pancreas adenocarcinomas possessed lymphoid cells cytotoxic to tumor target cells of either the small bowel or pancreas, but were not lytic to tumor tissue of ectodermal or mesodermal origin. Nor was injury inflicted upon normal intestinal, kidney, or tail fibroblastic cells, while significant lysis was seen when normal fetal cells were used as targets. The findings also suggest that the presence of the carcinogen in the assay has little influence upon the CMI values. Thus, the present investigation continues to support the concept that immunological responsiveness may serve as a useful measure for specifically identifying and quantitating effects of environmental carcinogens. (Author abstract) (23 Refs)

112. IDENTIFICATION OF CARCINOGENS BY MEASUREMENT OF CELL-MEDIATED IMMUNITY: III. IMMUNITY TO ASBESTOS-INDUCED RAT PERITONEAL MESOTHELIOMA.

Cole DA, Stevens RH, Will LA
(c/o Stevens) Dept. Radiology, Radiation Res. Lab., Univ. Iowa, Iowa City, IA, 52242
Environ Res; 28(1):77-83 1982

Antitumor cell-mediated immune (CMI) responses were detected in rats with asbestos (Canadian chrysotile B)-induced peritoneal mesotheliomas. The CMI was determined by in vitro lymphoid-cell cytotoxicity expressed by committed peripheral blood lymphoid cells (PBLC) obtained from the tumor-bearing animals toward cultured target cells of the tumors. Two apparently different target cell cultures which were developed from tumors of the same rat, one with epithelioid and the other with fibroblastic morphology, were lysed to the same degree by the sensitized PBLC. Specificity was observed for the PBLC reactivity as no cytotoxicity was expressed toward target cells derived from tumors of either ectodermal or entodermal origin. Nor were PBLC obtained from rats bearing tumors of these two tissue types capable of expressing injury to the mesothelioma target cells. These findings indicate that immune responsiveness developed to mesothelioma and suggest that such measurements might be useful for detecting environmental exposures to asbestos fibers. (Author abstract) (16 Refs)

113. A COMPARATIVE STUDY OF THE EFFECTIVENESS OF DIFFERENT MITOGENS FOR KARYOTYPIC ANALYSIS IN CHRONIC B CELL LEUKEMIA.

Katz RL, Cork A, Cox I, Murphy SG, Trujillo JM
Dept. Cytopathology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. at Houston, 6723 Bertner, Houston, TX, 77030
Leuk Res; 6(2):183-195 1982

Karyotypic abnormalities were studied in nine patients (8 males, 1 female, 38-76 yr old, mean age 63 yr) with chronic lymphatic leukemia using a combination of T and/or B cell mitogens. Clinical and hematological data at the time of sampling are presented. Eight out of nine patients demonstrated the presence of the mu heavy chain either alone, or as noted in two patients, together with delta or gamma chain on greater than 60% of the cells counted. The DNA synthetic capacity of the heterogenous population of neoplastic B lymphocytes and residual lymphocytes was assessed by the uptake of tritiated thymidine following incubation with different mitogens. Phytohemagglutinin (PHA) proved to be an effective inducer following incubation at 3-and 6-day intervals. Chromosome damage (CD) was noted to occur with pokeweed mitogen, lipopolysaccharide from Escherichia coli, and PHA with no evidence of an increased predilection for any one mitogen to reveal more damage than another. CD took the form of chromatid breaks, isobreaks, acentric fragments, deletions, and translocations. In addition, dicentric, ring, triradial, and minute chromsomes were observed on occasion. The results of HLA typing in the patients revealed a high incidence of cells (56%) positive for the HLA-A33 antigen. The frequency of this antigen as compared with that found in a normal donor panel matched for racial and ethnic origin was significant. The HLA-A24 antigen was observed in 33% of the patients, compared with an expected frequency of 18% for this population. (22 Refs)

SUPPRESSOR CELL ACTIVITY

114. ANALYSIS OF IMMUNOSUPPRESSOR CELLS INDUCED BY IMMUNIZATION OF SOLUBILIZED TUMOR-ASSOCIATED ANTIGENS PREPARED FROM A RAT FIBROSARCOMA.

Minami A
Dept. Orthopedic Surgery, Sch. Medicine, Hokkaido Univ., Sapporo, Hokkaido, Japan
Nippon Seikeigeka Gakkai Zasshi; 55(8):779-792 1981

Soluble tumor antigens were prepared from chemically-induced rat fibrosarcoma KMT-17 cells by sodium deoxycholate (DOC) extraction. Significant responses detected by the footpad assay and Winn assay were demonstrated in rats immunized with DOC extract. However, rats previously immunized with DOC extract showed a significant enhancement of tumor growth when challenged with KMT-17 cells. This enhancement was specific for the tumor line used. The tumor-neutralizing ability of KMT-17 immune spleen cells was abrogated when DOC extract immune spleen cells were added to a mixture of KMT-17 cells and KMT-17 immune spleen cells. This suppressive activity of the spleen cells was diminished by the treatment with anti T serum and complement. After fractionation of DOC extract immune spleen cells by the Ficoll density gradient, the cells in the light layer showed an enhancing effect on tumor growth, whereas the cells in the heavier region of the gradient had an inhibiting effect. These results suggested that both immunosuppressor cells and cytotoxic cells were induced in rats immunized with DOC extract. (Author abstract) (29 Refs)

115. SUPPRESSOR T LYMPHOCYTES CONTROL THE DEVELOPMENT OF PRIMARY SKIN CANCERS IN ULTRAVIOLET-IRRADIATED MICE.

Fisher MS, Kripke ML
Cancer Biology Program, NCI, Frederick Cancer Res. Facility, Frederick, MD, 21701
Science; 216(4550):1133-1134 1982

Exposure of mice to ultraviolet radiation results in the development of suppressor T lymphocytes in lymphoid organs, followed by the appearance of primary skin cancers. The presence or absence of these suppressor lymphocytes determines whether or not primary cancers will develop in the ultraviolet-irradiated skin. This demonstrates the importance of immunological regulatory pathways in carcinogenesis and provides an example of immunological surveillance. (Author abstract) (18 Refs)

116. REGULATION OF IN VITRO CYTOTOXIC T LYMPHOCYTE GENERATION: II. DEMONSTRATION OF NONCYTOTOXIC ALLOANTIGEN-SPECIFIC SUPPRESSOR T LYMPHOCYTES.

Schwartz A, Sutton SL, Gershon RK
Dept. Surgery, Tufts Univ. Sch. Veterinary Medicine, 350 South Huntington Ave., Boston, MA, 02130
Eur J Immunol; 12(5):380-386 1982

Both allospecific suppressor T lymphocytes (TSS) and nonspecific suppressor T lymphocytes (TSN) are activated in alloantigen-stimulated mixed leukocyte cultures (MLC). TSS and TSN can suppress cytotoxic T lymphocyte (CTL) induction upon transfer to fresh (second) MLC stimulated by the same alloantigens as in the first MLC (TSS) or (TSN) or by third-party alloantigens (TSN only). Evidence that TSS and TSN functions are performed by different T cell sets has been restricted to radioresistance of the former but not the latter. Separation of TSS from CTL has proven even more difficult. Methods are reported here which have allowed in vitro induction and functional separation of TSS from CTL and TSN in a totally allogeneic system. TSS are resistant to combined exposure to pyrilamine, a histamine 1 antagonist and local anesthetic, during suppressor cell induction, and to X or gamma irradiation thereafter, while CTL precursors (CTL-P) and TSN are more sensitive to such treatments. This allowed us to use these treatments to generate TSS that are not contaminated with functional CTL, CTL-P or TSN. These data show that TSS regulate CTL induction by interacting with responding cell populations, rather than by cytotoxic depletion of stimulator cells. (Author abstract) (40 Refs)

117. SUPPRESSOR MACROPHAGES IN TUMOR-BEARING MICE. INCONSISTENCY BETWEEN IN VIVO AND IN VITRO FINDINGS?

Forni G, Giovarelli M, Lanfrancone L, Varesio L
Dept. Microbiology, Univ. Turin, Via Santena 9, 10126 Turin, Italy
Int J Cancer; 29(6):695-698 1982

The growth of a spontaneous adenocarcinoma (ADK-1t) of BALB/c mice (H-2d, M1sb) induces progressive hyporesponsiveness of spleen cells stimulated with PHA or irradiated leukocytes from DBA/2 strain (H-2d, M1sa) in mixed leukocyte culture. This hyporesponsiveness is due to the suppressor activity of macrophage-like cells, since it is abrogated by passage over nylon-wool columns, pretreatment with carrageenans, or carbonyl iron and magnet. BALB/c mice bearing greater than 20 mm mean diameter ADK-1t tumors, and displaying a drastic impairment of T lymphocyte reactivity in vitro, were challenged with the P815 mastocytoma of the DBA/2 strain. These mice rejected increasing numbers of P815 cells to the same extent as normal BALB/c mice. The reactivity towards P815 is abrogated by 450 rad, and can be reconstituted by the adoptive transfer of 2 x 10(7) normal T lymphocytes in either normal or ADK-1t bearing BALB/c mice These data show that a discrepancy exists between the capacity of T lymphocytes from ADK-1t bearing mice to react against DBA/2 cells tested in vitro or in vivo, and indicates that great caution should be exercised in predicting the responsiveness of the immune system on the basis of in vitro data on the suppressor activity of macrophages. (Author abstract) (19 Refs)

OTHER RELATED STUDIES

118. CYCLOSPORIN-A IS SELECTIVELY CYTOTOXIC TO HUMAN LEUKEMIC T CELLS IN VITRO.

Totterman TH, Danersund A, Nilsson K, Killander A
Dept. Tumor Biology, Wallenberg Lab., Box 562, S-751 22 Uppsala, Sweden
Blood; 59(5):1103-1107 1982

We have studied the antileukemic effects of cyclosporin-A (CyA) on the cells of a number of human hematopoietic biopsies and established cell lines in vitro. CyA killed the tumor cells but not the nonmalignant control cells from three of four patients with T-lymphocytic leukemia/lymphoma at concentrations comparable to those recommended in clinical long-term immunosuppressive therapy. The leukemic cells from 7 days with B-type chronic lymphocytic leukemia were insensitive to

CyA. The drug was cytostatic and cytolytic to three of five T-lymphoblastic leukemia cell lines tested. With the possible exception of a plasma cell line, all other control cell lines (B-lymphocytic lymphoma, histiocytic lymphoma, fibroblast, and glia cell lines) were resistant to CyA. These observations indicate that CyA or its derivatives may be useful as a highly selective antitumor agent in different T-cell malignancies. (Author abstract) (33 Refs)

119. CHARACTERISTICS OF HODGKIN'S DISEASE-DERIVED CELL LINES.

Diehl V, Kirchner HH, Burrichter H, Stein H, Fonatsch C, Gerdes J, Schaadt M, Heit W, Uchanska-Ziegler B, Ziegler A, Heintz F, Sueno K
Hamatologie/Onkologie, Medizinische Hochschule, Karl-Wiechert-Allee 6, 3000 Hannover, W. Germany
Cancer Treat Rep; 66(4):615-632 1982

In the last 3 yr we were able to establish five long-term in vitro cell cultures from biopsy specimens taken preterminally from four patients with histologically proven Hodgkin's disease (nodular sclerosing type, clinical Stage IVB). Four of the lines are continuously proliferating in vitro; one culture stopped growth for unknown reasons after 7 months. When culture conditions were modulated, the first culture, L 428, gave rise to two sublines: L 428 KS, after adaptation to calf serum, and L 428 KSA, permanently growing as an adherent monolayer line after treatment with a phorbol ester (12-O-tetradecanoylphorbol-13-acetate) for 3 wk. Cell-marker analysis by conventional means (SIg, cIg, rosette formation, Epstein-Barr virus reactivity, cytochemistry, phagocytosis, and lysozyme production) and with monoclonal antibodies directed against various human lymphoid, myeloid, and monocytoid antigens showed that the tested cell lines are clearly different from all hitherto described hematopoietic lines; they most likely represent a cell type resembling an early myeloid-monocytoid progenitor cell. Conditioned medium of the L 428 cells and its two sublines showed colony-stimulating factor activity and suppression of spontaneous cell-mediated cytolysis of L 428 KS and K 562 cells. (Author abstract) (26 Refs)

120. PHENOTYPIC HETEROGENEITY OF HUMAN T-CELL MALIGNANCIES: DEMONSTRATION BY MONOCLONAL ANTIBODIES AND CYTOCHEMICAL MARKERS.

Knowles DM, Halper JP, Machin GA, Byeff P, Mertelsman R, Chess L
Lab. Surgical Pathology, Columbia Univ. coll. Physicians and Surgeons, 630 West 168th St., New York, NY, 10032
Am J Hematol; 12(3):233-245 1982

The present study sought to delineate the phenotypic heterogeneity of the human T-cell malignancies. Twenty T-cell neoplasms were investigated for reactivity with the OKT hybridoma monoclonal antibodies and expression of acid alpha-naphthyl acetate esterase (ANAE), beta-glucuronidase (BG), and acid phosphatase (AP) activity. Twelve cases (Mycosis fungoides, Sezary syndrome, cutaneous T-cell lymphoma, chronic lymphocytic leukemia) were OKT3+T4+, ie, expressed the phenotype commonly associated with mature T-helper cells. These cases were further divisible into ANAE+BG+ (6 cases), ANAE-BG+ (5 cases), and ANAE-BG- (1 case) phenotypes. In contrast to the 12 OKT3+T4+ cases, the remaining 8 cases showed considerable inter- and intratumor heterogeneity with respect to reactivity with the OKT antibodies. Six of these cases (acute lymphoblastic leukemia, lymphoblastic lymphoma) expressed phenotypes consistent with various intrathymic stages of T-cell differentiation. Five of the latter six cases were AP+BG+ANAE-, analogous to the majority of normal cortical thymocytes; an OKT3+T4-T8+T10+ neoplasm was ANAE+, analogous to normal medullary thymocytes. Two cases expressed the previously undescribed OKT3+T4-T8-T10+ phenotype. These studies demonstrate that the T-cell malignancies are divisible into phenotypes which correspond to normal maturational stages of T-cell differentiation and functionally distinct T-cell subsets. Phenotypic analysis of the human T-cell malignancies may provide a basis for understanding their biological heterogeneity and may aid in the identification of transitional stages of T-cell differentiation and minor T-cell subsets. (Author abstract) (21 Refs)

121. GRANULOPOIESIS IN BDF1 MICE TRANSPLANTED WITH L1210 LEUKEMIC CELLS.

Kuriya SI
Third Dept. Internal Medicine, Nippon Medical Sch., Tokyo, Japan
Nippon Ketsueki Gakkai Zasshi; 45(1):75-81 1982

The mechanism of granulocytosis in BDF1 female mice transplanted with L1210 leukemic cells was studied in detail. After aseptic injection of L1210 cells into the peritoneal cavity, granulocyte counts in circulating blood, granulocyte-macrophage stem cells measured as colony forming units in agar (CFU-C) in the bone marrow and spleen, and colony stimulating activity (CSA) of ascites were followed. In addition, influences on normal BDF1 bone marrow CFU-C of L1210 cells and the conditioned medium prepared by incubation of L1210 (L1210-CM) were studied in vitro. Granulocyte counts in the circulating blood began to increase 4 days after transplantation of L1210 cells and continued to rise till the animals died. The peak of CFU-C was attained on Days 3 and 5, respectively, in the bone marrow and spleen. Ascites of Days 6 and 7 contained definite CSA. L1210 cells and L1210-CM enhanced granulocyte-macrophage colony formation from normal murine bone marrow in vitro. Their enhancing activity was greatly lowered in the culture system where adherent cells were removed from both L1210 cells and bone marrow cells. It is concluded that L1210 leukemic cells stimulate murine CFU-C through CSA, resulting from their interaction with adherent cells, and cause granulocytosis. (Author abstract) (15 Refs)

122. MONOCLONAL IMMUNOGLOBULIN-SECRETING LYMPHOMA IN A PATIENT WITH SEVERE COMBINED IMMUNODEFICIENCY DISEASE.

Shirley LR, Buckley RH, Borowitz MJ, Welt SI, Kostyu DD
(c/o Buckley) Dept. Pediatrics, Duke Univ. Sch. Medicine, Box 2898, Durham, NC, 27710
Clin Exp Immunol; 48(3):666-674 1982

A 3.5 yr old boy with X-linked severe combined immunodeficiency disease (SCID), who had been in laminar flow isolation throughout his life, developed a B cell tumor producing up to 3,008 mg/dl of the IgM kappa paraprotein 1 mo after infusion of both liver and thymus cells from a fetal donor and 6 mo after the last of six fetal liver cell infusions given over a 3 yr period. Pretransplant studies revealed a high percentage of circulating B lymphocytes. HLA typing suggests that the tumor was of host origin. (Author abstract) (20 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Abe E	72
Abeatici S	12
Abramson SL	27
Ackermann R	105
Ackermann R	34
Adams DO	79
Adler WH	88
Adolf W	74
Adolphs HD	22
Afanas'ev IuI	78
Ahumada JC	32
Akaza H	23
Andersen BL	101
Anderson RE	100
Anderson VA	68
Andreeff M	103
Angyal I	87
Anisimov VN	43
Arlin Z	103
Atkinson K	102
Atluru D	84
Aulika BV	77
Bakhshinian MZ	78
Bambara LM	28
Banerjee D	95
Barbers RG	69
Bassi R	32
Bastian HP	22
Baxter CS	62
Beatrice F	7
Benedetti Panic	30
Bengolea O	25
Berke G	82
Bernard A	20
Beverley PC	93
Billing R	90
Boon T	97
Boraschi D	73
Borowitz MJ	122
Boumsell L	20
Bowman WP	26
Brandrup F	101
Buckley RH	122
Burchenal JH	37
Burrichter H	119
Bushinskaia LI	77
Bussi M	7
Bux P	65
Byeff P	120
Catalona WJ	76
Cauda R	30
Cavallo GP	7
Cawley JC	93
Celebrano R	28
Cerottini JC	97
Chang LJ	26
Chang LY	8
Chassagne J	20
Chess L	120
Chiao JW	103
Chigira M	45
Chilosi C	28
Christensen BE	101
Clark A	106
Clark W	82
Clark-Lewis I	98
Cole DA	108
Cole DA	111
Cole DA	112
Collins NH	96
Collins WM	60
Cook JL	82
Coppola A	24
Cork A	113
Corrocher R	28
Cortesina G	7
Cox I	113
Crisp D	18
Danersund A	118
Davies M	55
Davis F	86
Daynes RA	59
De Sandre G	28
Demeocq F	20
Depiante-Depaol	25
Di Fortunato V	7
Di Luzio NR	80
Di Roberto P	30
Diehl V	119
Dolinskaia SI	77
Dow LW	26
Dray S	64
Droller MJ	70
Ducluzeau R	54
Dunlop WR	60
Dupont B	96
Erdmann T	40
Fairchild D	53
Fekete B	87
Ferrarini M	10
Fidler IJ	75
Fisher MS	115
Fisher RI	33
Fleit HB	94
Fonatsch C	119
Forbes G	42
Ford RJ	86
Forni G	117
Forrai I	87
Fouchard M	52
Fray A	54
Freitag WB	103
Fulton RA	36
Gagne I	52
Gerdes J	119
Gerosa MA	4
Gershon RK	116
Ghio R	10
Giovarelli M	117
Goehle S	102
Goldfarb RH	50
Goldstein G	102
Golstein P	89
Gomolka D	70
Goos M	15
Gordon J	42
Gordon J	68
Grimm EA	58
Grnager DL	82
Grossmann H	19
Guyre PM	60
Haliotis T	67
Halliday WJ	46
Halper JP	120
Hamlet SM	99
Hammerstrom J	85
Hanna M	82
Hansen JA	102
Hara T	23
Harris AW	98
Hattori K	14
Hayot B	89
Hecker E	74
Heckl W	105
Heintz F	119
Heit W	119
Helfand SL	67
Henkart P	50
Herberman RB	50
Hibbs J	50
Hibbs JB	82
Hirose M	92
Hosli P	52
Hudemann B	40
Iakimova ER	77
Iakovleva IM	78
Ikawa T	16
Inoue Y	104
Irmscher J	19
Jennings PA	99
Johnson DW	84
Jonsson V	101
Kadin ME	107
Kapelner SN	24
Kapoor AK	1
Kataoka T	41
Katz RL	113
Keist R	74
Keller R	74
Khan IU	1
Khavinson VKh	43
Killander A	118
Kimura M	13
Kirchner HH	119
Kiremidjian-Sch	81
Klavins JV	8
Klebanoff SJ	57
Klein E	91
Kleinerman ES	61
Knowles DM	120
Kobayashi K	23
Kokelj F	31
Kondo N	17
Konstantinova I	77
Koseki K	23
Kostyu DD	122
Kotzsch M	19
Kripke ML	115

Kuriya SI 121
Kusumoto S 5
Laghi V 30
Lamvik J 85
Lanfrancone L 117
Laughter AH 27
Lavin MF 99
Leijh PC 29
Lemerle J 20
Levis P 12
Lewin D 53
Lewis AM 82
Lilleyman JS 110
Lindner A 21
Lindner A 47
Litvinov NN 77
Lloyd KO 96
Lucero K 90
Machin GA 120
Madgar I 21
Madgar I 47
Maebara S 45
Mahaley MS 4
Mahaley MS 48
Maizel AL 86
Many M 21
Many M 47
Margariti PA 30
Marino PA 79
Martinelli L 28
Maryanski JI 97
Mastro AM 56
Masucci G 91
Masucci MG 91
Maziere JC 52
Mazumder A 58
Mehrotra RM 1
Mehta S 86
Meisternst E 15
Melief CJ 39
Melvin SL 26
Menezes J 35
Menzio P 7
Merkur'eva RV 77
Mertelsman R 120
Mickshe M 6
Minale P 10
Minami A 114
Minato K 92
Miyawaki T 17
Mokyr MB 64
Moore M 51
Morales A 109
Moreau C 54
Morel CJ 32
Morgan D 52
Morishima Y 96
Moriya N 17
Moroz C 21
Moroz C 47
Morozov VG 43
Morra B 7
Morris AG 51
Mukai M 17
Mukhambetova LK 77
Muller M 19
Munson A 63
Murphy SG 113
Mussa A 12
Nagaoki T 17
Nagase M 45
Nathan C 82
Nathan CF 57
Nelson DJ 81
Nelson DS 104
Nervo P 30
Neveu PJ 49
Niijima T 23
Nilsson K 118
Nocera A 10
Noguera CA 24
Nozdrin VI 78
Oettgen HF 37
Ogata S 96
Oh-hashi F 41
Olivi A 4
Opferkuch HJ 74
Ottenhof PC 109
Pacheco-Rupil B 25
Pal A 87
Pascon G 32
Patel PC 35
Penn I 2
Pepin KG 56
Perdoux D 49
Perticarari S 31
Pezzutto A 4
Pierres M 89
Piguet H 9
Pilheu FR 32
Pistoia V 10
Plagne R 20
Poggio E 7
Potter CW 106
Potter MR 51
Presani G 31
Pross H 67
Pruzanski W 18
Przepiorka D 64
Ratliff TL 76
Rees RC 106
Reiss D 49
Rice L 27
Richard Y 20
Richter MA 95
Ritts RE 66
Roder J 67
Rosenberg SA 58
Rosenblum ML 4
Rosenthal CJ 24
Rothenberg E 71
Rothenborg HW 101
Rubin P 67
Rudiger KD 83
Ruiz-Arguelles 66
Sacco F 30
Sachno L 87
Sakurai Y 41
Salcman M 4
Samokhvalov GI 78
Sandrucci S 12
Sartoris A 7
Saxena QB 88
Saxena RK 88
Saxon A 69
Schaadt M 119
Schmidt R 74
Schmitz-Drager 105
Schmitz-Drager 34
Schoof RA 62
Schrader JW 98
Schreiber D 83
Schwartz A 116
Schwartz RS 39
Scully C 38
Semenzato GP 4
Seroogy KB 66
Seyfarth M 40
Shapiro A 76
Shapiro SH 8
Sherris D 59
Shi BJ 90
Shih WW 69
Shimoyama M 92
Shirley LR 122
Shopp G 63
Siddiqui JS 1
Soldateschi D 73
Sone S 75
Sonta-Jakimczyk 11
Souteyrand P 36
Spangrude GJ 59
Spellman C 100
Sroczynska M 11
Steigleder GK 15
Stein H 119
Sterry W 15
Stevens RH 108
Stevens RH 111
Stevens RH 112
Stevenson GT 68
Storb R 102
Storta P 12
Stotzky G 81
Suda K 44
Suda T 72
Sueno K 119
Sugden PJ 110
Sutton SL 116
Tagliabue A 73
Takahashi H 17
Takenichi Y 45
Tamassy K 87
Tandon VK 1
Taniguchi N 17
Teale DM 106
Terasaki PI 90
Thivolet J 36
Thobie N 54
Thomas ED 102
Thomsen K 101
Timonen T 50
Tiwari MC 1
Tobiuch K 92
Tomeo A 32
Totterman TH 118
Trevino E 25
Trevisan G 31
Trujillo JM 113
Tsiatis AA 26
Tsoi MS 3
Tuteja N 1
Twaig S 21

Twig S. 47
Twomey JJ 27
Uchanska-Ziegle 119
Uchida A 6
Udagawa H 45
Umeda T 23
Unkeless JC 94
Unsgaard G 85
Vakulova LA 78
Van Furth R 29
Van Snick J 97
Van Zwet TL 29
Van den Barsela 29
Varesio L 117
Viallard JL 20
Villani L 30
Votiakov AV 77
Wagner H 19
Watanabe H 45
Watkins PJ 48
Welt SI 122
Werkmeister J 67
Wessely Z 8
Wheeler TM 27
White K 63
Will LA 112
Wirth MP 34
Wojcik Z 11
Woodruff M 42
Woosley RE 48
Worman CP 93
Wright SD 94
Wu YY 98
Yabata N 45
Yen A 53
Yong WK 46
Zagury D 52
Zhang HZ 58
Ziegler A 119
Zsigray RM 60
Zwelling LA 61

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In this issue:

- EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS 1-49
- EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS 50-66
- EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION 67-91
- THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE 92-102
- ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY 103
- RELATED BIOLOGY OF IMMUNE CELLS 104-113
- CMI METHODOLOGY 114-117
- SUPPRESSOR CELL ACTIVITY 118
- OTHER RELATED STUDIES 119

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. SEVERE ACQUIRED IMMUNODEFICIENCY IN EUROPEAN HOMOSEXUAL MEN.

Gerstoft J, Malchow-Moller A, Bygbjerg I, Dickmeiss E, Enk C, Halberg P, Haahr S, Jacobsen M, Jensen K, Mejer J, Nielsen JO, Thomsen HK, Sondergaard J, Lorenzen I
Dept. Medicine, Hvidovre Hosp., Univ. Copenhagen, Hvidovre, Denmark

Br Med J; 285(6334):17-19 1982

Four previously healthy Danish homosexual men developed Kaposi's sarcoma or opportunistic infections with fever of unknown origin and lymphadenopathy. One patient died of a Pneumocystis carinii pneumonia. Three patients had defective cell-mediated immunity with absent leukocyte interferon production and decreased proliferative response to mitogens and antigens. T lymphocyte helper subsets and natural killer cell activity were reduced. Unstimulated mononuclear cells produced leukocyte migration inhibitor factor. Two patients were sexual partners and three had never been to the USA, where cases of severe acquired immunodeficiency have been reported. Thus, the syndrome must also be suspected in European homo-

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sexual men who present with fever of unknown origin, opportunistic infections, or Kaposi's sarcoma. (Author abstract) (23 Refs)

2. DISSEMINATED KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Friedman-Kien AE, Laubenstein LJ, Rubinstein P, Buimovici-Klein E, Marmor M, Stahl R, Spigland I, Kim KS, Zolla-Pazner S
New York Univ. Medical Center, 530 First Ave., New York, NY, 10016
Ann Intern Med; 96(6,part1):693-700 1982

Nineteen cases from an epidemic of disseminated Kaposi's sarcoma in homosexual men were studied by clinical, virologic, immunologic, and genetic methods. The patients were all male homosexuals ranging in age from 29 to 52 yr, with histories of multiple sexually transmitted diseases and exposure to both prescription and recreational drugs. Sites of disease included skin (16 of 19 patients), lymph nodes (13 patients), gastrointestinal tract (12 patients), spleen (3 patients), and lung (1 patient). Most patients had elevated levels of serum immunoglobins, positive antibody titers to hepatitis A and B virus, cytomegalovirus and Epstein-Barr virus, and impairment of cell-mediated immunologic reactions. The frequency of HLA-DR5 in these patients was significantly elevated. Two of the 19 patients died. Although the precise cause of this epidemic is unknown, it is likely that a genetic predisposition, an acquired immunoregulatory defect, and one or more infectious agents and drugs may be involved. (Author abstract) (48 Refs)

3. EPSTEIN-BARR VIRUS-INDUCED DISEASES IN BOYS WITH THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME (XLP). UPDATE ON STUDIES OF THE REGISTRY.

Purtilo DT, Sakamoto K, Barnabei V, Seeley J, Bechtold T, Rogers G, Yetz J, Harada S, XLP Collaborators
Dept. Pathology and Lab. Medicine, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Am J Med; 73(1):49-56 1982

Analyses of 100 subjects with the X-lined lymphoproliferative syndrome (XLP) in 25 kindreds revealed four major interrelated phenotypes: infectious mononucleosis, malignant B-cell lymphoma, aplastic anemia, and hypogammaglobulinemia. Eighty-one of the patients died. Two male subjects were asymptomatic but showed immunodeficiency to Epstein-Barr virus (EBV). Seventy-five subjects had the infectious mononucleosis phenotype and concurrently, 17 subjects of this group had aplastic anemia. All subjects with aplastic anemia died within a wk. Aplastic anemia did not accompany hypogammaglobulinemia or malignant lymphoma phenotypes. Hypogammaglobulinemia had been detected before infectious mononucleosis in there subjects, after infectious mononucleosis in five subjects, and was not associated with infectious mononucleosis in 11 boys with hypogammaglobulinemia. In nine subjects infectious mononucleosis appeared to have evolved into malignant lymphoma; however, the majority of patients with malignant lymphoma showed no obvious antecedent infectious mononucleosis. One subject had infectious mononucleosis following recurrent malignant lymphoma. Twenty-six of 35 lymphomas were in the terminal ileum. Results of immunologic and virologic studies of 15 survivors revealed combined variable immunodeficiency and deficient antibody responses to EBV-specific antigens. Mothers of boys with XLP exhibited abnormally elevated titers of antibodies to EBV. Subjects of both sexes with phenotypes of XLP should be investigated for immunodeficiency to EBV. Persons with inherited or acquired immunodeficiency may be vulnerable to life-threatening EBV-induced diseases. (Author abstract) (26 Refs)

4. SUPPRESSOR CELL DEVELOPMENT PREDICTS FOR TUMOR RECURRENCE IN SURGICALLY RESECTED LUNG CANCER (MEETING ABSTRACT).

Harris JE, Braun DP
Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, 60612
Proc Am Assoc Cancer Res; 23:989 1982

Immunoregulation of phytohemagglutinin (PHA) responsiveness by glass adherent cells and prostaglandin synthesizing cells was measured in the perpheral blood mononuclear cells (PBMC) of surgically resected Stage I or Stage II lung cancer patients in longitudinal studies. The relationship between immunoregulatory cell function, immunocompetence and disease relapse was determined. Immunoregulatory activity was measure in PHA-stimulated cultures in the presence and absence of 2 ug/ml indomethacin and in the presence and absence of glass adherent cells. The patient population consisted of 30 patients ranging in age from 44-68 years who were studied at 3 month intervals following surgery for a period ranging from 6 months to 2 years. Of the 30 patients studied, 7 patients suffered clinically detectable disease relapse at either 3 months (1 pt), 6 months (1 pt) 9 months (3 pts) or 12 months (2 pts) following surgery. In each instance of disease relapse seen, an increase in immunoregulatory cell function to a level significantly different from normal was observed 3 months prior, or coincident with clinical confirmation of disease recurrence. In 5 patients, increased immunoregulatory function was associated with significantly depressed PHA responsiveness while in the remaining 2 patients, increased immunoregulatory function occurred in association with normal PHA responsiveness. In the 23 remaining patients studied who have not relapsed to date, 2 have demonstrated a change in immunoregulatory function to a level significantly different from normal which has persisted through 2 consecutive assessment points, 5 have demonstrated transient increases in immunoregulatory cell function, and 9 have demonstrated persistent normal levels of immunoregulatory cell function at each assessment point following surgery. These data suggest that the development of indomethacin-sensitive and glass-adherent suppressor cells may precede and predict for tumor recurrence in surgically resected lung cancer patients. (no Refs)

5. LEUKOCYTE MIGRATION INHIBITION INDUCED BY EPSTEIN-BARR VIRUS ANTIGENS. IMMUNITY IN INFECTIOUS MONONUCLEOSIS AND SOME IMMUNODEFICIENT AND IMMUNOSUPPRESSED STATES.

Szigeti R, Klein E, Masucci MG, Ernberg I, Svedmyr E, Klein G
II. Gyermekklinika, Semmelweis Orvostudomany Egyetem, Budapest, Hungary
Orv Hetil; 123(20):1217-1221 1982

Leukocyte migration inhibition (LMI) elicited by Epstein-Barr virus (EBV) antigens was studied in 13 patients with infectious mononucleosis (IM), 2 patients with chronic mononucleosis, 4 with sex-linked lymphoproliferative disease and in 12 patients with neoplastic diseases (5 with Hodgkin's disease, 6 with non-Hodgkin's lymphoma and 1 with chronic lymphocytic leukemia). Appreciable LMI was observed in the patients with IM in response to enriched early antigen-virus capsid antigen (EA/VCA) extracts. Similar LMI of mononucleosis type (sensitivity to EA/VCA and insensitivity to EBV nuclear antigen (NA)) was seen in chronic mononucleosis as well, while the patients with sex-linked lymphoproliferative disease failed to respond to any EBV antigens. Tumor patients with elevated EBV antibody titers either showed LMI similar to that seen in healthy, seropositive controls or LMI of the mononucleosis type. The findings suggest that an intact immune system is necessary for LMI to occur in response to EBVNA or to crude cellular extracts containing mainly EBVNA, while sensitivity to EA/VCA is present when the immune system is impaired to a certain extent. Late hypersensitivity reaction in vitro is absent in severe immunodeficiency or immunosuppression. (42 Refs) (In HUN)

6. LEUKOCYTE-DERIVED INTERFERON (ALPHA) IN HUMAN BREAST CARCINOMA. THE AMERICAN CANCER SOCIETY PHASE II TRIAL.

Borden EC, Holland JF, Dao TL, Gutterman JU, Wiener L, Chang YC, Patel J
K4/414, Wisconsin Clin. Cancer Center, 600 Highland Ave., Madison, WI, 53792
Ann Intern Med; 97(1):1-6 1982

A multi-institutional trials program was initiated to define the effects of interferons in disseminated human breast carcinoma. Interferon alpha, prepared from buffy coats, was administered intramuscularly at 3 X 10(6) U daily for an initial period of 28 days. Of 23 patients who entered the program, five had an objective partial response of 92 days mean duration at diverse sites of involvement. Patients who responded were significantly older ($p = 0.050$) than nonresponders. Dose escalation in eight patients did not result in any clear evidence of additional responses. Major toxicities were fatigue, anorexia with weight loss, and reversible leukopenia (less than 3.5 X 10(9) leukocytes/L in 16 patients). Natural killer cell and antibody-dependent cell-mediated cytotoxicity were significantly (p less than 0.05) enhanced 48 hr after interferon administration began but subsequently declined despite continued therapy. Serum beta2-microglobulin concentrations increased on Day 15 (p less than 0.05) and remained significantly elevated on Day 22 (p less than 0.005). Peak interferon titers (mean, 62 U) occurred 6 hr after interferon was started, varied widely between patients, and were higher and more persistent with dose escalation. Once an optimal dose is defined, prospectively randomized trials will define what role interferons may have in systemic therapy of breast carcinoma. (Author abstract) (29 Refs)

7. FRBRIN DEPOSITS IN HODGKIN'S DISEASE.

Harris NL, Dvorak AM, Smith J, Dvorak HF
(c/o H. F. Dvorak) Dept. Pathology, Beth Israel Hosp., Boston, MA, 02215
Am J Pathol; 108(1):119-129 1982

Fibrin deposits were observed in the involved lymph nodes and/or spleens of 15 patients with Hodgkin's disease by specific immunofluorescence and by electron microscopy. Two basic patterns of fibrin deposition were observed: (1) intercellular deposits, chiefly associated with nonneoplastic-appearing lymphoid cells and (2) deposits associated with the collagen fibers of young connective tissue. In addition, coarse fibrin deposits were observed in areas of necrosis, presumably a nonspecific finding. Fibronectin was also observed in intercellular areas, but staining was less intense than for fibrin. Fibrin deposits were also observed in 3 of 6 cases on non-Hodgkin's lymphoma, indicating that the finding is not an exclusive feature of Hodgkin's disease. The pathogenesis and possible significance of fibrin deposition in Hodgkin's disease are related to earlier observations of activation of the coagulation system in neoplasia and cell-mediated immunity and to the possible role of fibrin, fibronectin, and their breakdown products in angiogenesis and fibroplasia. (Author abstract) (38 Refs)

8. FETAL AND ONCOFETAL ANTIGENS. REGULATORS OF IMMUNE REACTIONS.

McCluskey DR
Dept. Haematology, Royal Victoria Hosp., Belfast, Northern Ireland
Med Hypotheses; 8(6):627-634 1982

Cellular immune system, fetal and oncofetal antigens, and the maternal-fetal relationship is discussed. Neoplastic transformation is associatied with expression of neoantigens, which are capable of stimulating an immune response, but also with re-expression of fetal antigens which appear to activate a variety of specific and non-specific suppressor mechanisms. In pregnant females and patients with choriocarcinoma, peripheral blood lymphocytes inhibited DNA synthesis of normal lymphocytes thus suggesting that in pregnancy and patients with trophoblastic tumors, altered lymphocyte immunocompetence may play a role in survival of the fetus and neoplasm respectively. (44 Refs)

9. DEPRESSED CELL MEDIATED IMMUNITY AND HYPERIMMUNOGLOBULINAEMIA IN PATIENTS WITH LYMPHOMAS.

Tuteja N, Kapoor AK, Rathi AK, Mehrotra RM, Kumar A, Kushwala MR
Clinical Immunopathology Unit, Dept. Pathology, K. G. Medical Coll., Lucknow, India
J Indian Med Assoc; 78(4):63-66 1982

The significant finding of the present study was the detection of impaired CMI and hyperimmunoglobulinemia in majority of the patients with lymphomas. Defects in CMI were evident even during early stages of the disease. It appeared that there is a definite need to boost up T-cell mediated responses and to control the overactivity of B-cell in these patients. Proper handling of the immune system by appropriate therapy might change the course of this disease. (Author abstract) (16 Refs)

10. IMMUNOLOGIC DISORDERS IN BREAST CANCER.

Grinevich IuA
Res. Roentgenoradiological and Oncological Inst., Kiev, USSR
Eksp Onkol; 4(3):40-43 1982

States of cellular and humoral immunity were evaluated in 372 women (258 greater than 40 yr old) with breast cancer. Among these patients, 56 were in Stage I, 112 were in Stage II, 146 were in Stage III, and 59 were in Stage IV. The proportion of T-lymphocytes showed a progressive decrease from 35.6% in Stage I to 33.5% in Stage II, 32.3% in Stage III, and 28.1% in Stage IV (compared with 47.5% in healthy controls). The patients also showed a progressive decrease in intensity of delayed hypersensitivity reaction to dinitrochlorobenzene, and the T-lymphocyte migration indexes in the patients in Stages I, II, III, and IV were 58.9%, 49.6%, 48.6%, and 46.9%, respectively, compared with 95.3% in the controls. The proportions of B-lymphocytes in the patients in Stages I, II, III, and IV were 8.6%, 8.2%, 9.4%, and 9.6%, respectively, compared with 13.6% in controls. The patients (especially those in Stages III and IV) showed an increase in IgA and IgG levels and a decrease in IgM level. The changes in humoral immunity were associated with inhibition of formation of specific bacterial antibodies and progressive increase in level of immune complexes. (18 Refs) (In RUS)

11. AUTOLOGOUS MIXED LYMPHOCYTE REACTION IN THE PERIPHERAL BLOOD AND PLEURAL EFFUSIONS OF CANCER PATIENTS.

Uchida A, Mickache M
Inst. Cancer Res., Univ. Vienna, A-1090 Vienna, Austria
J Clin Invest; 70(1):98-104 1982

T cells proliferate in response to autologous non-T cells in the autologous mixed lymphocyte reaction (AMLR). AMLR was impaired in the peripheral blood of patients with advanced lung cancer (4,159 +-3,878 delta cpm vs 11,221 +-4,156 delta cpm for normal donors) but normal or even higher in their malignant pleural effusions (13,257 +-7,075 delta cpm vs 10,870 +-5,013 delta cpm for nonmalignant control effusions). Blood T cells also failed to respond to autologous effusion non-T cells, while effusion T cells strongly responded to autologous blood non-T cells. The presence of blood T cells did not inhibit effusion AMLR of the same patients. A subset of T cells the form rosettes with autologous erythrocytes is found to proliferate in AMLR. The number of autorosette-forming cells was lower in blood T cells of cancer patients than in blood T cells of normal donors and in effusion T cells of the patients. After enrichment of autorosette-forming cells, there was no difference in AMLR of normal blood and cancer blood and effusions. These results indicate that the loss of AMLR in the blood of cancer patients is due to a reduction of number of autoreactive T cells and not to a defect of autologous stimulator non-T cells. (Author abstract) (31 Refs)

12. ALLOANTIGEN-INDUCED SUPPRESSOR- AND MEMORY CELLS IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Kabelitz D, Fink U, Reichert A, Rastetter J
Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Immunobiology; 161(5):457-463 1982

T cell function was evaluated in patients with B cell type of chronic lymphocytic leukemia (CLL). Unseparated peripheral blood lymphocytes (PBL) and T cells from CLL patients stimulated in a primary allogeneic MLR were able to inhibit significantly a second MLR between the original responder (CLL) and stimulator (normal PBL) cell donors. Furthermore, it is shown that T lymphocytes from patients with CLL develop immunologic memory during the course of a primary MLR as evidenced by an enhanced response in secondary MLR. These results are discussed with respect to recently described imbalances of T cell subpopulations in CLL. (Author abstract) (15 Refs)

13. LYSIS OF AUTOLOGOUS EPSTEIN-BARR VIRUS-INFECTED B CELLS BY CYTOTOXIC T LYMPHOCYTES OF RHEUMATOID ARTHRITIS PATIENTS.

Tsoukas CD, Carson DA, Fong S, Slovin SF, Fox RI, Vaughan JH
Dept. Clinical Res., Scripps Clinic Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037
Clin Immunol Immunopathol; 24(1):8-14 1982

Since B lymphocytes of patients with rheumatoid arthritis (RA) have a higher rate of Epstein-Bar virus (EBV)-induced transformation than normal B cells, we have investigated whether this phenomenon is related to defective cytotoxic T-cell control of emerging B-cell clones. We have studied the in vitro generation of cytotoxic T lymphocytes specific for antigens appearing on autologous B cells after EBV infection using lymphocytes from six patients with RA. Cytotoxic cells were generated by two cycles of stimulation with mitomycin C-treated autologous B cells, and their lytic activity was assessed against 51Cr-labeled targets. As previously reported for lymphocytes of normal individuals, RA cytolytic T lymphocytes were induced only by EBV-infected B cells, not by noninfected B cells, and expression of the cytotoxicity required EBV-transformed targets. After primary in vitro stimulation with autologous EBV-infected B cells, the RA cytotoxic cells expressed higher lytic activity than the normal counterparts, but the difference was not statistically significant (p greater than 0.1). However, after secondary in vitro stimulation both groups displayed similar cytotoxic activities. In the presence of complement, monoclonal antibodies OKT8 (characterizing cytotoxic/ suppressor cells), SC1, and OKT3 (characterizing most T cells) reduced cytotoxicity by 80-90%; antibody OKT3 also reduced the lytic activity by 68% in the absence of complement. We conclude that the higher EBV-induced transformation rate seen with RA lymphocytes is not explained by a deficiency in this EBV-specific cytotoxic T cell. (Author abstract) (29 Refs)

14. CELL-MEDIATED IMMUNITY IN CHRONIC MYELOCYTIC LEUKEMIA.

Hernandez P, Cruz C, Fernandez NL, Santos MN, Ballester JM
Instituto de Hematologia, e Inmunologia, Apartado 8070, Ciudad de La Habena 8, Cuba
Acta Haematol (Basel); 67(4):249-254 1982

Fourteen patients with chronic myelocytic leukemia were evaluated immunologically; no difference was found in mean lymphocyte percentage and absolute number between patients and healthy subjects. Four cases (28.5%) showed decreased percentage of T lymphocytes, while only two cases (14.2%) had decreased absolute T lymphocyte values. PHA transformation was decreased in 57% of the patients. Spontaneous transformation in the short-term cultures exceeded the normal range in 65% of the cases. All patients skin tested were found to be reactive. Most of the patients had defective cellular immune response in vitro, probably related with a qualitative defect in T lymphocyte subpopulations. It cannot be completely excluded that part of the observed lymphocyte depression was due to the busulfan. (Author abstract) (20 Refs)

15. TISSUE T-LYMPHOCYTES IN UNTREATED HODGKIN'S DISEASE. MORPHOLOGIC AND FUNCTIONAL CORRELATIONS IN SPLEENS AND LYMPH NODES.

Baroni CD, Ruco L, Uccini S, Foschi A, Occhionero M, Marcorelli E
IV Cattedra di Anatomia ed Istologia Patologica, Universita di Roma, 00161 Roma, Italy
Cancer; 50(2):259-268 1982

In the present study the number of E-RFC and the in vitro response to PHA and ConA were determined for lymphocytes obtained from spleens and lymph nodes of untreated HD patients. The results were correlated with tissue involvement and with the histological pattern of the disease. Our investigation has revealed; (1) involved spleens and lymph nodes contained a higher percentage of T-lymphocytes than uninvolved tissues. The difference was statistically significant for lymph nodes. (2) A statistically significant correlation was not found between T-lymphocyte numbers and histology. (3) Lymphocytes from uninvolved spleens were significantly more reactive to both mitogens than cells from involved spleens and control non-neoplastic spleens as well. (4) Similar results were obtained with lymph node lymphocytes; however a significant difference was observed only when cells were stimulated with ConA. (5) The difference in proliferative response between uninvolved and involved tissues was maximally expressed in MC and progressively decreased in NS and LP. (6) T-cell enrichment does not alter the difference between uninvolved and involved spleens. (7) Cells from uninvolved and involved spleens, cultured for 24 hr, maintained unchanged their proliferative capacity. In this study evidence is provided that in HD T-lymphocytes from uninvolved tissues are characterized by an increased reactivity to mitogens, whereas cells from involved tissues are normally responsive. (Author abstract) (37 Refs)

16. ULTRASTRUCTURAL PEROXIDASES AND IMMUNOLOGICAL MARKERS IN ACUTE ADULT LEUKEMIA: THERAPEUTIC APPLICATIONS.

Marie JP, Escribano L, Perrot JY, Boucheix C, Kayibanda M, Martyre MC, Cadiou M, Rosenfeld C, Zittoun R
(c/o Zittoun), Service d'Hematologie de l'Hotel-Dieu, 1, place du Parvis Notre-Dame, F 75181 Paris Cedex 04, France
Nouv Presse Med; 11(21):1603-1606 1982

In a retrospective study of 112 adult patients with acute leukemia (AL), the percentage of undifferentiated leukemia was reduced to almost 1% by an analysis of routine cytochemical reactions (PAS, peroxidase, esterases and esterase inhibition), B and T lymphocyte markers (IgS, E-rosettes, HuTLA) cALL antigen and ultrastructural detection of peroxidase activity (PO-ME). A simultaneous study of cALL antigen and PO-ME showed reciprocal exclusion of these markers, except in one case of mixed leukemia. Therapeutically, the value of these tests lies in that patients with typical PAS reaction and cALL antigen consistently respond to vincristine-corticosteroid treatment, whereas patients without cALL and with PO-ME are frequently resistant to that combination of drugs. (Author abstract) (15 Refs) (In FRE)

17. STUDIES OF THE FUNCTIONAL PROPERTIES OF ALLOSPECIFIC DR ANTIGEN EXPRESSED ON MELANOMA AND LANGERHANS. CELLS AS STIMULATORS OF PRIMARY ALLOGENEIC PROLIFERATIVE AND CYTOLYTIC RESPONSES (MEETING ABSTRACT).

Pollack MS, Chin-Louis J, Safai B
Sloan-Kettering Institute for Cancer Research, New York, NY
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

We have previously shown that most cultured human melanoma cell lines and all epidermal Langerhans cells express HLA-DR alloantigens that have the same serological specificities as peripheral blood B-lymphocytes from the melanoma cell or Langerhans cell donors and that allogeneic lymphocyte proliferative responses can be induced by all these cell types. Further studies now indicate that the induction of proliferative responses by both melanoma cells and Langerhans cells do not require the presence of monocytes. Highly purified E-rosette positive T cells which not not contain any detectable M-1 positive monocytes show even higher proliferative responses than do unseparated mononuclear cells. However, melanoma and Langerhans cells also show significant differences in relation to the functional expression of their DR determinants. Whereas DR positive melanoma cells show much weaker stimulation of proliferative responses by allogeneic lymphocytes than normal B-cells, freshly isolated Langerhans cells show much stronger stimulation. Also, although reduced stimulation in cases of stimulator cell-responder cell DR matching and the blocking effects of monoclonal and allospecific anti-DR antisera indicate that the DR antigens are highly associated with the proliferation stimulating structures of melanoma cells, Langerhans cells and peripheral blood-B lymphocytes, stimulation by the DR positive melanoma cells leads, in some cases, to the development of melanoma specific cytolytic responses but does not lead to the generation of cytotoxic effector cells directed against either HLA-A,B or HLA-DR target antigens of either the stimulating melanoma cells or HLA matched lymphocytes. These results provide additional evidence for the distinction of the serologically defined HLA-DR antigens from the HLA-D determinants that are defined by functional studies in mixed cell cultures. (no Refs)

18. ABNORMAL IMMUNOREGULATION IN PATIENTS WITH NON-HODGKIN'S MALIGNANT LYMPHOMAS. I. INCREASED HELPER FUNCTION OF PERIPHERAL BLOOD T LYMPHOCYTES.

Gajl-Peczalska KJ, Chartrand SL, Bloomfield CD
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN, 55455
Clin Immunol Immunopathol; 23(2):366-378 1982

T lymphocytes isolated from the blood of 24 newly diagnosed and 2 relapsed patients with non-Hodgkin's malignant lymphomas were studied for helper/suppressor activity in cocultures with allogeneic tonsillar B lymphocytes stimulated with pokeweed mitogen. The IgA, IgG, and IgM secretion was measured by double-antibody radioimmunoassay. In 85% of patients with B lymphomas their T lymphocytes produced a severalfold increase in immunoglobulin secretion when compared with age-matched healthy controls. By contrast in two cases of T lymphoma, suppression of immunoglobulin secretion was observed. The ratio of 'T helper'/'T suppressor' lymphocytes, as measured with monoclonal antibodies (OKT4/OKT8), were similar for patients and controls, and concanavalin A-induced suppression was equally good. However, small numbers of patient T lymphocytes provided good help, while control cells failed in these higher dilutions. Possible explanations of the increased helper activity of 'nonmalignant' T lymphocytes in B lymphomas as related to clinical features and the pathogenesis of B- versus T-cell malignancies are discussed. (Author abstract) (31 Refs)

19. CLINICAL STUDIES ON IMMUNOPOTENT ACTIVITIES IN THE SERA OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL).

Iguchi K, Akane H, Tanimoto Y, Matsuda T, Sakurai M, Izawa T, Nishioka K
Dept. Pediatrics, Mie Univ. Sch. Medicine, Tsu, Japan
Rinsho Ketsueki; 23(1):53-60 1982

Immunopotentiating activity of leukemic sera from 35 children with acute lymphoblastic leukemia was investigated with the aid of tests of phytohemagglutinin- (PHA), Concanavalin A-, or pokeweed mitogen-induced lymphocyte blastogenic response and a cell cytotoxicity assay. Prior to treatment of leukemia in the patients, lymphocytes from the peripheral blood of the patients had a lower stimulation index of PHA-blastogenesis rate than did healthy controls. A strong immunosuppressive activity was also observed for the sera from patients with T cell Type leukemia, suggesting that the serum immunosuppressive factors may act specifically on the T cell moiety. Following induction of remission, leukemic sera from patients treated greater than 6 mo enhanced PHA-induced lymphocyte blastogenesis. Leukemic cells that were treated with sera from patients in remission and treated with immunotherapy were cultured with peripheral mononuclear cells. A cytotoxic reaction was observed due to the sera. The enhanced effect due to the sera was associated with the serum level of antibodies against leukemia cells. This suggested that the sera of patients given specific immunotherapy contains antibodies that are a part of antibody dependent cell-mediated immunity. (18 Refs) (In JPN)

20. IMMUNITY AND HYPERSENSITIVITY IN HODGKIN'S DISEASE.

Leoni P, Marchegiani G, Montillo M, Centurioni R, Montroni M, Danieli G
Istituto di Patologia Speciale Medica e Metodologica Clinica, Universita di Ancona, Ancona, Italy
Minerva Med; 73(20):1361-1369 1982

Some immunological parameters (absolute count and percentage of lymphocytes, E rosettes and lymphocytes with S immunoglobulin (S-Ig)) were studied in 47 patients with Hodgkin's disease (HD). The percentages of lymphocytes were found to be 33% in Stage I, 26% in II, 21% in III and 20.7% in IV; 46% in lymphocyte predominant (LP) type, 22.3% in nodular sclerotic (NS) Type, 27.6% in mixed cellular (MC) Type and 24.6% in lymphocyte depleted (LD) Type. The percentages of E rosettes were 58% in Stage I, 50.8% II, 52% in III and 50% in IV; 35% in LP Type, 53.1% in NS Type, 46.6% in MC Type and 45.5% in LD Type. The percentages of lymphocytes with S-Ig were 17% in Stage I, 32% in II, 35.5% in III and 24.3% in IV; 22.9% in LP Type, 31.7% in NS Type, 30.5% in MC Type and 38% in LD Type. Functional and anatomic depression of the T-cell system is prevalent or exclusive in patients with Stages III and IV of HD of MC and LD Type. Studied on immunological changes and their causes in patients with HD are reviewed. (111 Refs) (In ITA)

21. IMMUNE COMPETENCE EVALUATION INCLUDING T-CELL SUBSETS IN PATIENTS (PTS) WITH LUNG OR HEAD AND NECK (H AND N) CARCINOMAS AND SMOKERS (SMK) (MEETING ABSTRACT).

Camacho ES, Schechter P, Graham R, Camacho SA
Jerry Pettis Veterans Administration Hospital, Loma Linda, CA, 92354
Proc Am Soc Clin Oncol; 1:C-156 1982

To determine if the immune abnormalities commonly reported in pts with smoking related tumors were also present in smk, we studied 16 pts with lung carcinomas (LC), 12 pts with H and N tumors at the time of diagnosis, before treatment, using 45 cancer free controls [29 smk and 16 non-smokers (n-smk)]. Tests of immune function performed were: total lymphocyte count, T cells by E-rosetting at 4 degrees, T-cell subsets by indirect immunofluorescence using monoclonal antibodies which identify helper/inducer (OKT4+) and suppressor/cytotoxic (OKT8+) populations, B cells quantitated with polyvalent antibodies, lymphocyte proliferation with phytohemagglutinin (PHA), and monocyte function by measuring light emission (chemiluminescence) after zymosan ingestion. No difference in lymphocyte count or T and B-cell percentages between cancer pts and controls was found. The percentage (%) of OKT4+ cells in LC pts (31.9) was lower than smk (39.8) and n-smk (47). H and N pts showed no difference from controls in the % of OKT4+ cells, but had a higher % of OKT8+ cells (27) when compared to smk (20). PHA response was depressed in LC pts [69,700 counts per minute (cpm)] and in H and N pts (68,800 cpm) when compared to smk (192,200 cpm) and n-smk (108,100 cpm). There was a trend of higher chemiluminescence in mononuclear cells of cancer pts when compared to controls which was significant only when comparing LC pts (40,121 cpm) to smk (25,605 cpm). In these tests cancer pts had a response pattern distinct from smokers and the latter were similar to non-smokers. (no Refs)

22. IMMUNE RESTORATION OF CANCER PATIENTS' GRAFT VERSUS HOST RESPONSE (GVHR) BY AZIMEXON IN VITRO (MEETING ABSTRACT).

Patt YZ, Talpaz M, Hersh EM, LaPushin R, Mavligit GM
M.D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Assoc Cancer Res; 23:967 1982

Azimexon, a cyanazaridinyl immunomodulator has been shown to reverse radiation-induced and cyclophosphamide induced leukopenia. In vivo studies in humans have shown restoration of delayed type hypersensitivity and increases in NK (natural killer) activity and response of T lymphocytes to mitogens. Anti-tumor activity was observed in melanoma patients (pts) given high doses of the agent. We decided to study this agent in vitro prior to the initiation of a phase I clinical trial using the GVHR. Peripherial Blood Lymphocytes (PBL) from 16 pts with solid tumors, were incubated with either medium alone or with 10 ug/ml of Azimexon. Normal donor PBL were used as simultaneous controls to verify adequate performance of the assay. A GVHR of less than 50 mm was considered negative. The median spontaneous GVHR volume among the cancer pts was 9.3 mm3 with 14 of 16 having a negative GVHR. Following incubation with 10 ug/ml of Azimexon, the GVHR has risen to 40.75 mm3, and in 6 of 14 pts with a negative GVHR it was restored to positive. Among normal controls GVHR was mostly positive and did not change significantly with in vitro Azimexon. We conclude that Azimexon may have immunorestorative capacity in pts with a negative GVHR. Clinical trials are currently being conducted to determine in vivo the immunomodulatory effects of the drug. (no Refs)

23. SPECIFIC IN VITRO ANTIBODY RESPONSES BY HUMAN BLOOD LYMPHOCYTES: APPARENT NONRESPONSIVENESS OF PBL IS DUE TO A LACK OF RECIRCULATING MEMORY B CELLS.

Callard RE, McCaughan GW, Babbage J, Souhami RL
Immunology Unit, Dept. Medicine, Univ. Sydney, Sydney 2006, Australia
J Immunol; 129(1):153-156 1982

Peripheral blood lymphocytes from a number of individual donors were tested for in vitro antibody production to influenza or herpes viruses. All donors were primed, yet a small proportion either failed to respond or responded very poorly when tested in vitro. Reconstitution experiments carried out with E- (B cells and monocytes) and E+ (T) cells showed that the inability of nonresponder cells to make antibody in vitro resided exclusively with E- cells. It was concluded that the defect was in the B cell compartment. This conclusion was supported by further reconstitution experiments using E- and E+ cells prepared from blood, spleen, and lymph nodes from the same donor. Blood E- cells from nonresponders failed to make antibody when combined with either blood, lymph node, or spleen E+ (T) cells. By contrast, E- cells from lymph nodes or spleens responded normally when recombined with E+ cells from spleen, lymph node, or blood. These experiments showed that nonresponsiveness resided within the B cell compartment, and moreover, that it was confined to the blood, ie, to the recirculating lymphocyte pool. Apparently, recirculating memory B cells may be sequestered, under some circumstances, from the blood to other lymphoid tissues. Patients with untreated Hodgkin's disease were also investigated. Blood lymphocytes from these patients failed to make antibody in vitro to influenza or herpes viruses, whereas spleen cells obtained during staging laparotomy responded well. Again, the defect in the blood was found to reside exclusively with the B cell compartment. In contrast to normals, blood lymphocytes from most Hodgkin's patients were unresponsive in vitro to several antigens. Thus, part of the pathology of this disease seems to be a lack of B cells in the blood that can make specific antibody in vitro. (10 Refs)

24. IMMUNOLOGICAL REACTIVITY IN CARCINOMA IN SITU OF THE BLADDER.

Hudemann B, Riedel H, Seyfarth M, Werner H, Erdmann T
Urologische Klinik, Wilhelm-Pieck-Universitat Rostock, Ernst-Heydemann-Strasse, DDR-2500 Rostock, E. Germany
Z Urol Nephrol; 75(4):253-257 1982

In vitro and in vivo immunological reactivities were studied in 13 patients with carcinoma in situ (CIS) of the bladder and in 29 controls. The patients with CIS did not differ from the controls in skin tests using five recall antigens and the primary antigen dinitrofluorobenzene. In electrophoretic tests, 11/13 CIS patients showed a slowing of lymphocyte mobility when the cells were incubated with bladder tumor-associated antigen; 10/13 showed a similar slowing of lymphocyte mobility when human encephalitogenic protein was used as the antigen. The findings suggested that CIS is the first stage in malignant degeneration. (14 Refs) (In GER)

25. PROGNOSTIC SIGNIFICANCE OF REACTIVE ALTERATIONS IN THE LYMPH NODES IN CARCINOMAS OF THE STOMACH AND BREAST.

Riegrova D, Jansa P
Katedra patologicke anatomie, LF UP, S. Allenda 3, 775 00 Olomouc, Czechoslovakia
Cesk Patol; 18(2):90-96 1982

Regional lymph nodes were examined in 80 patients (48 men and 32 women, 37-80 yr old) with adenocarcinomas of the stomach and in 70 women (30-81 yr old) with infiltrating carcinomas of the breast, and the findings were correlated with the length of survival. Regional lymph node metastases were found in 34/80 patients with gastric carcinomas and in 52/70 patients with breast cancer. Fifty-eight of the 80 patients with gastric carcinomas and 30/70 with breast carcinomas died within the first 3 yr. Seventeen patients (7 with and 10 without metastases) with gastric cancer and 30 (16 with and 14 without metastases) with breast cancer survived 5 yr or longer. Lymphocyte predominance combined with sinus histiocytosis was found to be a prognostically favorable sign in both groups, and prevalence of germ centers along with sinus histiocytosis was an additional favorable prognostic sign in the patients with gastric cancer. Lymphocyte depletion, especially in the absence of sinus histiocytosis, was a prognostically unfavorable sign. The presence of isolated lymph node metastases itself, without regard to the reactive type, could not be interpreted as unfavorable for survival time. (20 Refs) (In CZE)

26. ADENOSINE DEAMINASE ACTIVITY IN HODGKIN'S DISEASE.

Muller G, Krug K, Kruger W, Richter V, Rassoul F
II. Medizinische Klinik und Poliklinik, Martin-Luther-Universitat, Halle-Wittenberg, Leninallee 2, DDR-402 Halle, E. Germany
Klin Wochenschr; 60(6):317-318 1982

The activity of adenosine deaminase (ADA) (EC3.5.4.4) was determined in the blood plasma, erythrocytes, and lymphocytes of 23 patients with Hodgkin's disease and partly also in 99 control subjects. The enzyme activities were measured using adenosine as substrate and by analysis of ammonia. No correlation was found between the ADA activities in lymphocytes, erythrocytes, and blood plasma. The lymphocytes of the patients revealed lower ADA activities (U/g protein) than the lymphocytes of control subjects. The ADA activity is not reduced in plasma or erythrocytes. The lower activities of ADA in the lymphocytes of patients may be related to the impaired cell-mediated immunity of the Hodgkin's disease. (Author abstract) (14 Refs) (In GER)

27. IMMUNOSUPPRESSIVE EFFECT OF ACUTE-PHASE REACTANT PROTEINS IN VITRO AND ITS RELEVANCE TO CANCER.

Samak R, Edelstein R, Israel L
(c/o Israel) Laboratoire d'Immunobiologie des Tumeurs Humaines, Centre Hospitalier Universitaire Paris XIII, Hopital Avicenne, 125, route de Stalingrad, F-93000 Bobigny, France
Cancer Immunol Immunother; 13(1):38-43 1982

Several acute-phase reactant proteins (APRPs) were screened for their immunological effects to investigate immunosuppressive properties of serum from patients and animals with malignant disease. Concentrations used were determined by taking the highest levels observed in patients waith metastatic cancer, then preparing one-half, one-quarter, and one-eighth dilutions. In the lowest concentration tested (1), none of the proteins significantly modified the response of normal lymphocytes to the phytohemagglutinin (PHA). At concentration 2, haptoglobin and fibrinogen significantly decreased lymphocyte response. At the lowest concentration tested (2) none of the proteins significantly inhibited monocyte chemotactic migration. At concentration 3 orosomucoid became inhibitory, while at the highest concentration (4), both haptoglobin and fibrinogen became inhibitory. Orosomucoid, alpha1-antitrypsin, and ceruloplasmin did not significantly depress the blastogenic response individually at any of the concentrations tested nor when they were combined in concentration 1. When combined in concentrations 2-4, significant suppression of the blastogenic response was observed. The blastogenic response was maximal with a PHA dilution of 1/32. Preincubation of cells with a 1/32 dilution of PHA for 2 hr, followed by washing and postincubation for 46 hr with phosphate-buffered saline produced a significant blastogenic response. When the post-incubation was performed with fibrinogen (concentrations 3 and 4) significant suppression was observed. (22 Refs)

28. IMMUNE MODIFYING EFFECTS OF INDOMETHACIN ON PERIPHERAL BLOOD LYMPHOCYTES IN CANCER PATIENTS (MEETING ABSTRACT).

Wanebo HJ, Pace R, Marshall D
University of Virginia, Charlottesville, VA, 22908
Proc Am Assoc Cancer Res; 23:976 1982

Indomethacin (Indo) is considered to have immune modulating effects primarily by its prostaglandin inhibiting activity on suppressor adherent cells (macrophage). The effects of co-culturing indomethacin and lymphocytes stimulated with varying concentrations of phytohemagglutinin (PHA) or Staph Phage Lysate (SPL), were measured to define the range and pattern of responses in patients (pts) with different types of solid tumors. Indomethacin was incubated with lymphocytes which were stimulated by PHA or an antigen SPL, and blastogenesis recorded by counting 3H thymidine labelled cells. Indo concentrations ranged from 5x10(-4) ug/ul to 5x10(-2) ug/ul. Patients tested included 20 controls and 62 cancer patients (breast 17, colon 14, head and neck 22, and melanoma 9). Patients were not receiving therapy at the time of treatment. In general the positive responses ranged from 15% to 550% with PHA and up to 2000% with SPL. Indo augmented PHA responses in 19/60 (31%) pts, produced negative responses in 13/60 (22%), and no response in 47%. SPL produced significantly increased blastogenic responses in 46/55 pts. Indo produces defined effects on lymphocyte function which vary with concentrations of drug and lymphocyte stimulant. It appears to produce more consistent responses with an antigen than with a mitogen where it may have inhibitory effects. Indo may have a role as an immune modulator in cancer patients who are immunologically depressed. (no Refs)

29. IMMUNE RESPONSES IN PATIENTS WITH BRAIN TUMORS: FACTORS SUCH AS ANTI-CONVULSANTS THAT MAY CONTRIBUTE TO IMPAIRED CELL-MEDIATED IMMUNITY (MEETING ABSTRACT).

Neuwelt EA, Kikuchi K, Hill S, Lipsky P, Frenkel EP
Oregon Health Sciences University, Portland, OR, 97201
Proc Am Assoc Cancer Res; 23:982 1982

The responsiveness of lymphocytes obtained from patients with brain tumors to in vitro stimulation with mitogenic lectins was examined. The previously reported finding of decreased responsiveness was confirmed. To investigate the factors responsible for the hyporesponsiveness, mitogen (phytohemagglutinin and pokeweed mitogen) induced lymphocyte activation was evaluated using lymphocytes from 22 patients with brain tumors and 22 normal individuals. Lymphocytes from 13 patients with brain tumors, showed depressed responsiveness when cultured in autologous serum; in 8 this was marked and in 5 moderate. Normal, rather than autologous, serum corrected lymphycyte function from only one of the markedly hyporesponsive patients, suggesting the existence of an intrinsic lymphocyte abnormality in some patients with brain tumors. However, serum from the hyporesponsive patients depressed mitogen-induced activation of lymphocytes from both tumor patients and normal volunteers. The presence of suppressive serum factors could not be related to the nature of the tumor (benign versus malignant, site, cell type or degree of anaplasia). The present studies however did show that significant depression of in vitro lymphocyte responsiveness occurred with exposure to two anti-convulsant agents (phenytoin and phenobarbital) and dexamethasone. Thus, impaired lymphocyte function in patients with brain tumors may have a complex explanation with drug (corticosteroids, anticonvulsants) induced suppression playing a significant role. (no Refs)

30. MACROPHAGE-MEDIATED LYSIS OF NORMAL LYMPHOCYTES WITHIN HODGKIN'S DISEASE LYMPH NODES (MEETING ABSTRACT).

Frenster JH, Masek MA, Frenster DA
Department of Medicine, Stanford University, Stanford, CA, 94305
Proc Am Soc Clin Oncol; 1:C-134 1982

Phagocytic macrophages are prominent components of the normal cell response in Hodgkin's Disease, but correlate inversely with patient survival despite macrophage activity against neoplastic Hodgkin's Cells and Reed-Sternberg Cells. Lymph nodes positive for the nodular sclerosis type of Hodgkin's Disease were fixed in the operating room after biopsy during pathologic staging of newly-diagnosed patients, and were then analyzed by high-resolution transmission electron microscopy. Neoplastic Hodgkin's Cells and Reed-Sternberg Cells, and normal monosomal and polysomal lymphocytes, phagocytic macrophages, monocytes, eosinophiles, fibroblasts and endothelial cells were identified by ultrastructural criteria. Phagocytic macrophages were found to be preferentially apposed to normal lymphocytes, but while polysomal lymphocytes comprised a minority of all normal lymphocytes apposed by macrophages, they comprised a majority of all normal lymphocytes phagocytized by macrophages. Phagocytized lymphocytes were visualized within macrophages in all stages of cell lysis, from intact normal lymphocytes with high nuclear DNA template activity, to digested cells with low nuclear DNA template activity. Phagocytizing macrophages contained up to four separate phagocytized lymphocytes, but neoplastic Hodgkin's Cells and Reed-Sternberg Cells were only apposed but not phagocytized by macrophages. (4 Refs)

31. IMMUNITY IN PATIENTS WITH KIDNEY CANCER.

Mokhort VA, Mavrichev AS, Aleksa TV
Urological Clinic, Byelorussian Inst. Advanced Training for Physicians, Minsk, USSR
Urol Nefrol (Mosk); (3):16-20 1982

The state of antitumor immunity was studied in 95 patients with primary kidney cancer (Group 1), 19 patients with postoperative metastases or recurrences of kidney cancer (Group 2), and in 33 clinically cured patients (Group 3). The patients in Groups 1 and 2 showed progressive decrease of leukocyte and lymphocyte counts and increase of monocyte count. The patients in Group 3 had normal leukocyte and lymphocyte counts and elevated monocyte count. Skin tests showed reduced reaction to phytohemagglutinin (PHA), tuberculin, and embryonal antigen and increased reaction to tumor-associated antigen in the patients in Groups 1 and 2, while the patients in Group 3 had normal response to PHA and tuberculin and lack of response to embryonal and tumor-associated antigens. The changes in the functional activity of the immunocompetent cells depended upon the stage of the disease. The decrease of the indices of cellular immunity was associated with stage-dependent elevation of parameters of humoral immunity. (11 Refs) (In RUS)

32. DEMONSTRATION OF HISTIOCYTES IN THE EPIDERMAL INFILTRATE OF MYCOSIS FUNGOIDES.

Kerdel FA, Morgan EW, MacDonald DM
(c/o MacDonald) Lab. Applied Dermatopathology, Guy's Hosp., London SE1, England
Br J Dermatol; 106(6):651-656 1982

The presence of histiocytes in the epidermal and dermal infiltrate of mycosis fungoides was observed histochemically by revealing a diffuse pattern of acid alpha-naphthyl acetate esterase (ANAE) activity in the cytoplasm, and immunohistochemically by demonstrating the presence of histiocyte-specific 'enzymes', lysozyme, alpha-I-antitrypsin and alpha-I-antichymotrypsin. Histiocytes in the infiltrate of mycosis fungoides may be involved in antigen processing and interaction with T lymphocytes. (Author abstract) (36 Refs)

33. QUANTITATION WITH MONOCLONAL ANTIBODIES OF LEUKOCYTE SUBSETS IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF SOLID TUMOR PATIENTS (MEETING ABSTRACT).

Harris JE, Vahey AL, Braun DP
Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, 60612
Proc Am Soc Clin Oncol; 1:C-165 1982

Percentages and numbers of monocytes and subsets of T cells recognized by monoclonal antibodies were measured in the peripheral blood of solid tumor cancer patients (pts) and correlated to levels of immunocompetence. The population studied consisted of 25 pts with disseminated solid tumors, 20 pts with surgically resected minimum residual disease and 35 normal individuals. Peripheral blood mononuclear cells (PBMC) were analyzed by indirect immunofluorescence for reactivity with monoclonal antibodies which recognize monocyte associated determinants (OKM1 and BRL63D3); and monoclonal antibodies which recognize T cells, helper/inducer T cell subsets and cytotoxic/suppressor T cell subsets (OKT3, OKT4 and OKT8, respectively). Immunocompetence was assessed in Phytohemagglutinin (PHA)-induced lymphocyte DNA synthesis assays. When patient data was grouped according to stage of disease, no significant differences from normal were seen in percentages of OKT3, OKT4 and OKT8 cells in PBMC from all cancer pts, minimum residual disease pts or disseminated disease pts. In pts with advanced disease a significant decrease in absolute numbers of lymphocytes, OKT3 cells, OKT4 cells and OKT8 cells was seen, reflecting the absolute lymphopenia of these pts. A significant increase was seen in the percentages of PBMC reacting with OKM1 and BRL63D3 from advanced disease pts compared with normal donors or localized disease pts. A positive correlation was found between PHA responsiveness and absolute numbers of OKT3 and OKT4 cells. A negative correlation was found between PHA responsiveness and percentages of OKM1 cells. These data indicate that malignant disease does not alter T cell subset percentages in cancer pt peripheral blood. Percentages of OKM1 and BRL63D3 cells are increased in advanced solid tumor pts in association with impaired PHA responsiveness. (no Refs)

34. CYTOTOXICITY OF HUMAN PULMONARY ALVEOLAR MACROPHAGES (PAMS) FROM PATIENTS WITH LUNG CANCER (MEETING ABSTRACT).

Kan-Mitchell J, Hengst JC, Kempf RA, Brooker AS, Adelson LJ, Rothbart RK, Simons SM, Mitchell MS
University of Southern California Cancer Center, Los Angeles, CA, 90033
Proc Am Assoc Cancer Res; 23:1038 1982

The functions of human PAMs have been relatively little studied compared with those of their circulating counterparts, blood monocytes. This study examined the ability of human PAMs to kill primary human tumor cell cultures, and control primary fibroblasts, in an in vitro cytotoxicity assay. PAMs were derived by bronchial lavage from patients with lung cancer, noncancerous disorders, and subjects with a presumed illness that proved benign. After extensive washing the PAMs were cocultured with 3H-proline labeled target cells, principally lung cancers and melanomas, at various effector:target ratios for 72 hrs. Cytotoxicity was measured by comparing residual radioactivity in the wells with adherent tumor cells cultured in the presence or absence of PAMs. PAMs from 7 of 7 patients with cancer and 6 of 8 chronic pulmonary conditions were active against one or more tumor targets even at low effector:target ratios. These PAMs were inactive against fibroblasts. However, PAMs from 5 of 5 individuals who proved normal were noncytotoxic. Extracted human leukocyte interferon (IFN-alpha) enhanced killing with 3 of 4 specimens from cancer patients. IFN had no effect on PAMs from 3 normal subjects, and 2 patients with active sarcoidosis and preexistent high levels of killing. However cytotoxicity was induced by IFN in noncytotoxic PAMs from 2 sarcoid patients with inactive disease. In summary, human PAMs from patients with lung cancer or chronic active pulmonary diseases were cytotoxic to several recently explanted tumor cells in vitro. Normal PAMs and those from inactive sarcoidosis were not. Cytotoxicity could be modulated by IFN in vitro. (no Refs)

35. IN VITRO ANTITUMOR ACTIVITY OF HUMAN BLOOD MONOCYTES AGAINST CULTURED HUMAN CANCER CELLS.

Konishi K
Dept. Otorhinolaryngology, Niigata Univ. Sch. Medicine, Niigata 951, Japan
Nippon Jibiinkoka Gakkai Kaiho; 85(2):107-121 1982

Anti-tumor activity of human blood monocytes was examined in vitro against Okajima stomach cancer (OSC), Kato III stomach cancer (KSC), and Hattori breast cancer (HBC) cell lines. Monocytes were obtained from 10 healthy subjects (24-38 yr old), 33 patients (29-82 yr old) with malignant tumors of the head and neck region, and 10 patients (20-68 yr old) with chronic inflammatory diseases. Antitumor activity was assessed with the aid of 51Cr-release assay and 3H-thymidine incorporation test. Antitumor activity of peripheral blood monocytes from the healthy control subjects was demonstrated only with the 3H-thymidine test, suggesting that the antitumor activity was primary due to inhibition of proliferation. Antitumor activity was enhanced by in vitro treatment of the monocytes with Propionibacterium acnes, P acnes-cell wall skeleton, picibanil, and Nocardia-rubra-cell wall skeleton but not by polysaccharide Kureha. Monocytes from umbilical blood and peripheral blood monocytes from the cancer patients had the same antitumor effects as the monocytes from the control subjects. The immunopotentiators also enhanced the antitumor activity of the monocytes from the cancer patients. (68 Refs) (In JPN)

36. INTERFERON MODULATION OF HUMAN MONOCYTE CYTOLYTIC FUNCTION (MEETING ABSTRACT).

Huard TK, Solvay MJ, LoBuglio AF
Simpson Research Institute, University of Michigan, Ann Arbor, MI, 48109
Proc Am Assoc Cancer Res; 23:974 1982

We have examined the in vitro effects of human interferon (IFN) on the cytolytic potential of human peripheral blood monocytes. Direct tumor cell killing was assessed in a 3H-thymidine (3H-TdR) release assay after 48, 72 and 96 hr of incubation. Fc-receptor dependent cytotoxic function was measured in a 4 hr 51 Cr-release antibody dependent cellular cytotoxicity (ADCC) assay. Monocyte suspensions were prepared by harvest from adherent monolayers and were greater than 85% non-specific esterase positive and greater than 95% monocytes by morphology. For the direct assay, varying numbers of monocytes were co-incubated with 2x10(4) HeLa or K-562 target cells to produce E/T ratios of 10:1 to 1:1. The direct addition of IFN-beta to this assay produced no change in cytotoxicity (300-2000 u). These doses of IFN-beta incubated with tumor cells alone produced dramatic cytostasis without cytolysis. Preincubation of monocytes in teflon lined tubes with IFN-beta for 18 hrs produced a 2-5 fold enhancement of direct monocyte cytotoxicity. Optimal enhancement of cytotoxicity was observed with 300 U/1x10(6) monocytes and was evident at effector/target cell ratios as low as 3:1. Highly pure recombinant HuIFN-alpha produced an augmentation of monocyte tumoricidal activity quite similar to the crude IFN-beta. Monocyte ADCC to normal O+ (R1R2) human RBC was also enhanced 2-4 fold by HuIFN-beta. This was observed for RBC sensitized with alloantisera to either Rh-D or Rh-CD antigens. Monocyte ADCC to human CEM T-lymphoblasts, however, was not altered by Hu-IFN-beta. Inhibition of monocyte ADCC by soluble monomeric human IgG was comparable between control and IFN-treated monocytes. Thus, both the crude HuIFN-beta and the recombinant bacterial HuIFN-alpha have potent effects on the cytolytic capacities of human monocytes in vitro. (no Refs)

37. DIMINISHED AUTOLOGOUS MIXED LYMPHOCYTE REACTION IN PATIENTS WITH HODGKIN DISEASE: EVIDENCE FOR NON-T CELL DYSFUNCTION.

Zamkoff KW, Dock NL, Kurec AS, Davey FR
Dept. Medicine, Upstate Medical Center, 750 East Adams St., Syracuse, NY, 13210
Am J Hematol; 12(4):327-335 1982

In the autologous mixed lymphocyte reaction (AMLR), T lymphocytes are stimulated to proliferate by autologous non-T mononuclear cells. In five untreated patients with Hodgkin disease, the AMLR was diminished. In addition, in the same five patients, T cell response to PHA was inhibited by a cell in the non-T cell fraction, the response of non-T cells to PWM was diminished, and there was a diminished ability of the non-T cell population to stimulate in allogeneic MLR. However, the response of T cells from patients with Hodgkin disease to allogeneic antigen was normal. The AMLR and allogeneic MLR were then studied in an additional five untreated patients before and after monocyte depletion of the stimulating non-T mononuclear cell population. In this second group of Hodgkin disease patients, the AMLR was again diminished when T cells were incubated either with non-T cells or non-T cells depleted of monocytes. In the Hodgkin patients, monocyte depletion did not alter the T cell response in the AMLR. In the controls, monocyte depletion greatly diminished the proliferative response. The diminished AMLR in untreated Hodgkin disease patients mey be the result of a failure of adequate monocyte stimulation of autologous T cells. (Author abstract) (20 Refs)

38. DEPRESSED T CELL PROLIFERATIVE RESPONSES IN HODGKIN'S DISEASE (HD): ROLE OF MONOCYTE-MEDIATED SUPPRESSION VIA PROSTAGLANDINS AND HYDROGEN PEROXIDE (MEETING ABSTRACT).

Fisher RI, Bostick-Bruton F
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:988 1982

Increased production of prostaglandins by suppressor monocytes has been reported to cause depressed proliferative responses in HD. These studies were performed to assess the importance of the monocyte suppression and the role of prostaglandins and hydrogen peroxide as potential mediators. As expected, mononuclear leukocytes (MNL) from 22 untreated HD patients had lower proliferation after stimulation with a suboptimal dose of phytohemagglutinin (2ug/ml) than 30 age and sex matched normal controls. When optimal doses of indomethacin (1ug/ml) were added to cultures, the mean percent increase for patients exceeded that of controls but patient proliferation remained only 36% of normal. Since hydrogen peroxide is produced by activated monocytes, catalase (2500 u/ml) was added to patient cultures with minimal effect. However, when catalase plus indomethacin were added to patient cultures, a synergistic increase was observed although patient proliferation remained subnormal. Removal of adherent monocytes produced increases in proliferation comparable to that observed after indomethacin. Long term disease free survivors of HD had depressed proliferation but did not have significant increases after addition of indomethacin compared to normals. We conclude 1) although excessive prostaglandin production contributes to depressed proliferation in untreated HD, it is not the major cause; 2) hydrogen peroxide contributes to depressed proliferation in untreated HD and normals; 3) depressed proliferative responses in cured HD are not mediated by prostaglandins; and 4) other factors, probably inherent to the T cell itself, are the major cause of depressed proliferation in HD. (no Refs)

39. OPPOSING EFFECTS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES ON THE GROWTH OF CULTURED LEUKEMIA CELL LINES.

Carlquist JF, Ford C, Alley L
Dept. Pathology, LDS Hosp., 325 8th Ave., Salt Lake City, UT, 84143
Cell Immunol; 69(2):381-387 1982

Natural killing of two human leukemia cell lines (K562 and Molt 4) in a soft-agar, clonogenic assay was shown to be the result of two opposite yet concurrent processes: target cell colony stimulation and inhibition. The stimulatory effect was demonstrable when the effector lymphocytes and target cells were separated in contiguous agar layers, suggesting mediation by a soluble factor. Similarly, stimulation occurred when the effector lymphocytes and target cells were combined at low effector-target cell ratios that do not favor direct cell contact. Target colony inhibition was found to be dominant when large E:T ratios were employed. Both target-effector binding and natural killing were significantly reduced in medium devoid of divalent cations. (Author abstract) (10 Refs)

40. MECHANISMS OF HUMAN CELL-MEDIATED CYTOTOXICITY. II. CORRECTION OF THE SELECTIVE DEFECT IN NATURAL KILLING IN THE CHEDIAK-HIGASHI SYNDROME WITH INDUCERS OF INTRACELLULAR CYCLIC GMP.

Katz P, Roder JC, Zaytoun AM, Herberman RB, Fauci AS
(c/o Fauci), Natl. Inst. Allergy and Infectious Diseases, NIH, Building 10, Room 11B-13, Bethesda, MD, 20205
J Immunol; 129(1):297-302 1982

In this study, we investigated the modulation by cyclic nucleotides of depressed natural killer (NK) cell activity in two patients with the Chediak-Higashi syndrome (CHS). Patients with CHS have defective NK function that is not attributable to a lack of effector cells or a defect in target cell binding. Because of the previously reported abnormalities of the levels of intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) in these patients, we investigated the effects of exogenous cGMP or its intracellular inducers on CHS NK activity. This study further underscores the importance of cyclic nucleotides as regulators of normal and abnormal NK activity and may be useful in developing means of increasing defective lytic activity in CHS patients and those individuals with demonstrable abnormalities of natural killing. (24 Refs)

41. FURTHER STUDIES OF NATURAL KILLER CELL FUNCTION IN CHEDIAK-HIGASHI PATIENTS.

Roder JC, Haliotis T, Laing L, Kozbor D, Rubin P, Pross H, Boxer LA, White JG, Fauci AS, Mostowski H, Matheson DS
Dept. Microbiology and Immunology, Queen's Univ., Kingston, Ontario K7L 3N6, Canada
Immunology; 46(3):555-560 1982

Spontaneous natural killer (NK) activity and antibody-dependent cellular cytotoxicity (ADCC) of blood lymphocytes against five human tumor cell lines (K562, Molt-4, HL-60, Chang, Daudi) and three mouse tumor lines (YAC, P815, RBL-5) were 10-to 100-fold lower than normal in six patients with Chediak-Higashi (CH) disease. NK and ADCC were defective at 4 hr, and less so at 18 hr. The NK activity in normals and CH patients was mediated in part by FcR+, E- effector cells. ADCC against human erythrocytes was normal in CH patients, as were lectin-dependent cytolysis and mixed lymphocyte proliferative responses. Phagocytosis of antibody-coated ox erythrocytes was normal in CH patients as well. These observations confirm that the CH syndrome is associated with a profound and selective defect in NK and ADCC activity against tumor cells, whereas other mononuclear cell-mediated functions are normal. (Author abstract) (10 Refs)

42. NK ACTIVITY AND ITS RADIORESISTANCE IN LEUKEMIA AND BONE MARROW TRANSPLANTATION (MEETING ABSTRACT).

Schecter B, Brovall C, Polmar S, Pierce G, Coccia P
Case Western Reserve University, Cleveland, OH
Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

Natural killer (NK) activity may play a role in immune modulation, GVHD (graft verus host disease) and in viral infections. We have evaluated NK activity, and its resistance to gamma irradiation in leukemic patients in remission under evaluation for bone marrow transplantation (BMT) and following engraftment of HLA identical bone marrow. NK activity of peripheral blood mononuclear cells (PBMNC) of 11 patients with acute leukemia was slightly lower than 11 control subjects (x +/- SEM patients: 18.2% +/-4.2%, controls: 27.0% +/-4.1%, p equals .08). Radioresistance of NK activity is controlled by an X linked gene. Ten of eleven patients were radiosensitive by genotyping. Residual NK activity (RA) after 3000 rads of 10 sensitive control subjects was 13.8% +/-1.9% of unirradiated activity; in 10 leukemia patients RA equals 41.7% +/-8.1% (p equals .003) suggesting recruitment of a cell expressing radioresistant NK activity in the leukemics in remission. NK activity and its radiosensitivity was evaluated post-BMT in 9 patients: 7 leukemics, a child with Ewing's sarcoma and a child with SCID (severe combined immunodeficiency disease). The SCID patient, who received without ablation an HLA-A, B, C, D matched buffy coated infusion from a maternal grandfather, showed lymphoid engraftment documented by improved immunological function, marrow and blood karyotype and mild liver GVHD. Conversion of the granulocyte genetic markers did not occur. Conversion of NK radioresistance phenotype did occur. Conversion of NK radioresistance phenotype occurred in 1/2 discordant leukemic recipient/donor pairs. NK activity and radioresistance in the immediate post-transplant period was evaluated with regard to GVHD and viral infection. In 10 assays of 6 patients, engrafted with sensitive donors, RA of greater than 30% after 3000 rads was positively associated with documented Varicella-Zoster virus (VZV) infection (py less than .025) and not associated with GVHD. NK activity of lymphocytes stimulated in vitro is radioresistant. These data are consistent with the non-myeloid, bone marrow origin of spontaneous NK activity and the recruitment of other cells expressing radioresistant NK activity in leukemia and in VZV infection post-BMT. (no Refs)

43. CYTOTOXIC T CELLS IN CYTOMEGALOVIRUS INFECTION. HLA-RESTRICTED T-LYMPHOCYTE AND NON-T-LYMPHOCYTE CYTOTOXIC RESPONSES CORRELATE WITH RECOVERY FROM CYTOMEGALOVIRUS INFECTION IN BONE-MARROW-TRANSPLANT RECIPIENTS.

Quinnan GV, Kirmani N, Rook AH, Manischewitz JF, Jackson L, Moreschi G, Santos GW, Saral R, Burns WH
Div. Virology, Office Biologics, Bureau Drugs and Biologics, Food and Drug Admin., 8800 Rockville Pike, Bethesda, MD, 20205
N Engl J Med; 307(1):7-13 1982

Prospective studies were conducted of cell-mediated cytotoxic response in 58 recipients of syngeneic or allogeneic bone-marrow grafts. Emphasis was placed on the period 4-12 wk after transplantation, when the risk of cytomegalovirus (CMV) infection is greatest. Forty-three patients had CMV during the period of study; 23 patients survived infection. CMV infection was the principal cause of death in 12 patients, and an additional 8 patients died from other causes during acute CMV infection. A significant rise in cytotoxicity was observed early in the course of infection, as measured by CMV-specific cytotoxic lymphocyte response. Evidence of CMV-specific cytotoxic response was found in all patients who survived infection. Patients with nonfatal infections showed significantly greater response than those with fatal infections. The natural-killer-cell activity of lymphocytes from patients with nonfatal infections was within the normal range both before and after the onset of infection, but in the group with fatal infection, lower than normal activity was observed in 4 patients before the onset of infection and in 11 patients afterward. Neither the presence nor level of complement-fixing antibodies in donors or recipients before transplantation correlated with the risk of infection or the likelihood of recovery. The finding that the capacity for cytotoxic response, mediated both by HLA-restricted T lymphocytes and nonrestricted non-T lymphocytes during CMV infection, correlated with recovery strongly suggests that these effector cells mediate recovery from CMV infection. (32 Refs)

44. NATURAL KILLER CELLS (NK) IN RESISTANCE TO LEUKEMIA AND VIRUSES IN BONE MARROW TRANSPLANT (BMT) RECIPIENTS (MEETING ABSTRACT).

Ching C, Lau W, Wong L, Paik Y, Jim R, Wilkinson R, Miller C, Loh K, Seto D. Yoshitsugi H, Ching N
University of Hawaii-Cancer Center of Hawaii, Honolulu, HI, 96813
Proc Am Assoc Cancer Res; 23:1063 1982

In BMT recipients, normal pre-tranplant NK(HSV-1), a herpesvirus injected fibroblast target, has correlated witn the subsequent development of graft-versus-host disease (GVHD). Reports by others, of NK(K562), a leukemia cell, appear to differ. Thus, NK(K562), NK(HSV-1) and to normal fibroblast, NK(FS) were examined in 12 patients with hematopoietic malignancies. NK function was deficient in all 7 patients with acute leukemia in relapse, 3 with aplastic anemia (AA), normal in 2 in remission. Human leukocyte interferon (IFNalpha) in vitro augmented NK in 2 AA, and acute myelocytic leukemia (AML) in remission, and not in patients in relapse. Six patients received BMT from an HLA identical sibling. Five patients who developed GVHD had low pre-transplant NK or NK cells inducible by IFNalpha, except for one in complete remission. NK post-BMT was normal with one exception. In an AML patient with severe GVHD, NK cells killed non-specifically both fibroblast targets: NK(FS) 15%, NK(HSV-1) 31%. NK was normal in patients surviving viral infections. CMV-interstitial pneumonitis was fatal in 1 patient with low NK(HSV-1) 6%, NK(FS) 1%, NK(K562) 20%. His lymphocytes treated with IFN alpha did not increase NK(HSV-1), NK(FS); NK(K562) increased from 20% to 33%. This patient had 1% large granular lymphocytes (LGL). These studies support a biological role for NK function in resistance to leukemia and viral infections in immunodeficient patients. (no Refs)

45. SUSCEPTIBILITY OF TUMOR CELLS TO LYSIS MEDIATED BY HUMAN NATURAL KILLER (NK) CELLS (MEETING ABSTRACT).

Paciucci PA, Ohnuma T, Alter BP, Lassus M, Holland JF, Wasserman LR
Mt. Sinai School of Medicine, New York, NY, 10029
Proc Am Assoc Cancer Res; 23:1059 1982

NK cells are a subset of peripheral blood lymphocytes (PBL) with cytolytic activity against some tumor cell lines in vitro. Differentiated (D) tumors are reported to be less resistant to NK cell mediated cytotoxicity than less mature cells. Three undifferentiated tumor cell lines and 2 melanoma lines were evaluated as targets for NK cells obtained from healthy persons and the 2 melanoma patients. K562 and HL-60 leukemic cell lines were D in vitro with hemin and retinoic acid, respectively. Induction with these agents yielded 95% terminally D cells by day 5; MOLT-3 (T-cell ALL) was cultured with supernatant obtained from activated human mixed leukocyte cultures. K562 and HL-60 and their respective D lines were equally and highly susceptible to lysis. Cytotoxicity against MOLT-3D was greatly decreased from that observed against the undiffferentiated line; treatment of PBL with human leukocyte interferon (IF) in part restored cytotoxicity against MOLT-3D. The 2 melanoma lines were lysed by fresh allogenic PBL, whereas they were resistant to lysis mediated by autologous NK cells. Treatment of PBL with IF not only resulted in a 2-to 3-fold increase of lysis against the susceptible targets, but also in augmented cytotoxicity against the autologous melanoma cells, from 8.0% and 4.3% to 26.3% and 23.2%, respectively, at an effector/target ratio of 50:1 in a 4-hr 51Cr release assay. (no Refs)

46. ANTITUMOR EFFECTS OF MALTOSE TETRAPALMITATE (MTP): RESULTS ON PHASE I STUDY AND ON THE PREVENTION OF TUMOR METASTASIS (MEETING ABSTRACT).

Nigam V, Bonaventure J, Ibrahiem EH, Kappany H, Brailovsky C, Elhilali M
University of Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada
Proc Am Assoc Cancer Res; 23:961 1982

MTP was shown by us to be non toxic immunoadjuvant superior in its action to clinically used immunoadjuvants. Synergy was demonstrated between tumor surgery or tumor chemotherapy and MTP treatment. We have now conducted phase I studies in a group of 7 placebo treated and 9 MTP treated human volunteers. There was no clinical, biochemical or hematologic manifestation of toxicity due to MTP given orally twice weekly for 4 weeks at 5 mg dose level. Higher doses are under study. In animal experiments, when various doses ([illegible]-100 ug/day) of MTP were given in drinking water to sc implanted prostatic adenocarcinoma (R3327 A) or orthotopically implanted bladder cancer bearing rats, there was reduced tumor growth by low and high doses of MTP. High dose MTP (100 ug/day) also reduced lymph node (14% for treated vs 44-90% for controls) and lung (35% for treated vs 66-83% for controls) metastasis. Since experiments using 3H labelled MTP given orally demonstrate its localization in certain organs especially lymph nodes, lung, liver, spleen and tumor, it would indicate that the compound is not degraded at the intestinal level. The fact that MTP is not directly cytotoxic to tumor cells, strongly suggests that mode of action of MTP is via liberation of factors from MTP activated macrophages. Recent results obtained with macrophage supernatants support this hypothesis. (2 Refs)

47. RECOVERY OF COLONY FORMING UNITS-GRANULOCYTE, ERYTHROCYTE, MEGAKARYOCYTE, MACROPHAGE (CFU-GEMM) FOLLOWING CRYOPRESERVATION, AND PRELIMINARY CORRELATION WITH MARROW RECOVERY FOLLOWING AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) (MEETING ABSTRACT).

Knight WA, Roodman GD, Bell BS, Wright TL, Newcomb TF
University of Texas Health Science Center, San Antonio, TX, 78284
Proc Am Assoc Cancer Res; 23:630 1982

Though marrow engraftment after ABMT nearly always occurs, in vitro CFU assays have not correlated well with marrow recovery following transplantation. We have examined the effects of cryopreservation on the recovery of single cell origin colonies containing the four major elements, CFU-GEMM among 13 patients (Pts) undergoing marrow storage for subsequent ABMT. Using the method described by Ash, et al marrow aliquots were assayed for CFU-GEMM prior to cryopreservation. Marrow was mixed with 10% dimethylsulfoxide (DMSO), autologous plasma, and tissue culture media, then frozen at-1 C/min to-40 C, and-2 C/min to-80 C. Specimens were stored at-196 C in the liquid phase of nitrogen. Post-freeze specimens were rapidly thawed, washed to remove DMSO, and plated. Time between storage and post freeze assay varied from 5 to 149 days. Median pre and post freeze CFU-GEMM assays were 13 colonies/10(5) cells (Range(R):3-28) and 8 colonies/10(5) cells (R:1-25) respectively. Median percent recovery was 100 (R:4-170). Three patients have had L-phenyl-alamine mustard, 180 mg/M2 and ABMT with similar numbers of cryopreserved nucleated marrow cells. Two had 100% CFU-GEMM recovery post freeze, and marrow engraftment (WBC greater than 1000, PLTS greater than 50,000) on days 19 and 15. One patient with 10% CFU-GEMM recovery did not reconstitute until day 27. (1 Ref)

48. EVALUATION OF BENZALDEHYDE(BA) AS A CHEMOTHERAPEUTIC AGENT (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:784 1982

Benzaldehyde is a naturally occurring compound extracted from figs and released during bacterial degradation of amygdalin (Laetrile) that has been reported to have anti-tumor activity. We have tested BA as benziladine glucose against a variety of human tumors in vitro and against human tumor xenografts. BA was tested over a concentration range of 0.1 to 100 ug/ml against human marrow granulocyte/macrophage progenitors (CFU-GM) and showed dose-dependent inhibition at 10-100 ug/ml. HL60 promyelocytic leukemia colonies were significantly more sensitive than CFU-GM at concentrations of 50 and 100 ug/ml. However, HL60 cells were not inhibited by BA in liquid culture, and KG-1 myelocytic leukemia colonies were resistant to the drug. B-CLL colonies from 2 pts were also resistant to BA. When administered to athymic mice bearing human tumor xenografts at doses of 25 or 50 mg/kg, BA had no effect on tumor growth or non-tumor weight of a colon carcinoma (T380) or an epidermoid carcinoma (T222). Colonies of T222 cells and an astrocytoma xenograft grown in agar were resistant to BA. Histologic sections of T380 and T222 tumors and cytospins of HL60 cells exposed to BA showed no evidence of increased differentiation. Human tumor colony forming units grown from biopsies of 10 pts (7 ovarian, 1 breast, and 1 epidermoid carcinoma and 1 medullablastoma) were tested against BA. Only 1 ovarian carcinoma showed greater than 70% inhibition at 100 ug/ml. (no Refs)

49. CELL-MEDIATED IMMUNITY TO MOUSE MAMMARY TUMOR VIRUS ANTIGENS BY PATIENTS WITH HYPERPLASTIC BENIGN BREAST DISEASE.

Cannon GB, Barsky SH, Alford TC, Jerome LF, Tinley V, McCoy JL, Dean JH
Immunotoxicology Section, Litton Bionetics, Inc., 5516 Nicholson Lane, Kensington, MD, 20795
JNCI; 68(6):935-943 1982

Peripheral blood leukocytes of patients with preoperative breast cancer, benign breast disease, and benign gynecologic disorders and normal healthy females were tested, as blind coded specimens, with murine mammary tumor virus (MuMTV) antigens in the direct and indirect leukocyte migration inhibition (LMI) assays. The incidence of reactivity by patients with breast cancer was low. (From 5 to 35% breast cancer patients reacted, depending on which group of control individuals they were compared to and what antigen was used.) Nonparametric analyses showed no differences between control groups (normal donors and patients with gynecologic disorders) and breast cancer patients with either assay. However, there was a significant difference between benign breast disease patients with hyperplasia and (1) benign breast disease patients without hyperplasia (p less than 0.03) and (2) patients with gynecologic disorders (p less than 0.040) in the direct assay when it was performed blindly with the gp52 antigen. Patients with hyperplasia (benign breast disease as well as breast cancer) had a higher incidence of enhanced migration in the indirect test than breast disease patients without hyperplasia. The enhanced migration to the MuMTV was correlated to enhanced migration to a 3-M KCl extract of the breast cancer cell line MCF-7 in simultaneous tests. Thus the LMI assays with MuMTV antigens do not appear valuable in breast cancer diagnosis, but they may help to identify a small group of benign breast disease patients whose breast pathology is thought to be associated with a high risk for developing breast cancer. (Author abstract) (20 Refs)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

50. IMMUNOPATHOLOGY OF B-CELL LYMPHOMAS INDUCED IN C57BL/6 MICE BY DUALTROPIC MURINE LEUKEMIA VIRUS (MULV).

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Am J Pathol; 107(3):362-377 1982

Combined clinicopathologic and immunomorphologic evidence is presented that would indicate that a murine leukemia virus (MuLV) with the dualtropic host range is capable of producing a clinically malignant lesion composed of immunoblasts and associated plasma cells in C57BL/6 mice. This process, morphologically diagnosed as an immunoblastic lymphoma of B cells using standard histopathologic criteria, was found to be distinctly polyclonal with regard to immunoglobulin (Ig) isotype when analyzed for both surface and cytoplasmic Ig. Further studies demonstrated that this clinicopathologically malignant, dualtropic MuLV-induced, polyclonal immunoblastic lymphoma of B cells in C57BL/6 mice was normal diploid and unable to be successfully transplanted to nonimmunosuppressed syngeneic recipients. Although all serum heavy and light chain components were found to be progressively elevated as the tumor load increased, the polyclonal increase in serum immunoglobulins was most pronounced for mu heavy and kappa light chains (ie, mu greater than gamma2A greater than alpha greater than gamma 2B greater than gamma1; kappa greater than lambda). The dissociation of clinicopathologic and biologic criteria for malignancy in the presently described dualtropic (RadLV) MuLV-induced B-cell lesion is sharply contrasted with the thymotropic (RadLV), MuLV-induced T-cell lymphoblastic lymphoma in C57BL/6 mice. This process is also a clinicopathologically malignant lesion but, when one uses biologic criteria, is found to be distinctly monoclonal, aneuploid, and easily transplanted to nonimmunosuppressed syngeneic recipients. The close clinicopathologic and biologic similarities of the dualtropic MuLV-induced animal model to corresponding human B-cell lymphoproliferative diseases are stressed. (Author abstract) (46 Refs)

51. TUMOR IMMUNITY IN RAT LYMPH NODES FOLLOWING TRANSPLANTATION.

Rabson JA, Geyer SJ, Levine G, Swartz WM, Futrell JW
Div. Plastic Surgery, Univ. Pittsburgh Sch. Medicine, 1117 Scaife Hall, Pittsburgh, PA, 15261
Ann Surg; 196(1):92-99 1982

Inguinal lymph nodes in the Buffalo rat were autotransplanted to the popliteal fossa by an intact vascular pedicle or by microvascular anastomosis. These revascularized nodes had normal histology and made spontaneous afferent and efferent lymphatic reconnection with surrounding lymphatic vessels, as documented by ink and silicone rubber injection studies. Lymphoscintigraphy with 99mTc antimony sulfide colloid correctly predicted the 44 of 120 node transplants that had made afferent reconnection. To demonstrate immunologic activity of lymph nodes following transplantation, a cellular adherence assay was employed to detect cell-mediated cytotoxicity of lymph node cells isolated from rats sensitized to an allogeneic gliosarcoma. Cytotoxicity was detected in nontransplanted regional nodes sensitized to tumor (p less than 0.01) and in nodes transplanted by vascular pedicle and then sensitized to tumor (p less than

0.001). This study demonstrates that lymph nodes can be transplanted with restoration of functional lymphatic anatomy, and that following transplantation, lymph nodes retain the ability to mount an immune response against tumor. (Author abstract) (26 Refs)

52. SPECIFIC IMMUNOTHERAPY COMBINED WITH WHOLE BODY IRRADIATION OF BALB/C MICE BEARING MOLONEY MURINE SARCOMA VIRUS-INDUCED PRIMARY TUMORS.

Kimura H, Yamaguchi Y, Fujisawa T
Dept. Surgery, Inst. Pulmonary Cancer Res., Sch. Medicine, Chiba Univ., Inohana 1-8-1, Chiba 280, Japan
Gan; 73(3):446-453 1982

Adoptive transfer of lymphocytes was performed into mice bearing progressor Moloney murine sarcoma virus (M-MSV)-induced primary tumors. Lymphocytes from mice immunized against M-MSV (designated as immune lymphocytes, IL) inhibited tumor growth when transferred before the virus injection. However, the same lymphocytes were ineffective against tumors consisting of a solid mass when transferred after the virus inoculation. When IL was transferred shortly after 500 rad whole-body irradiation of the tumor-bearing mice, tumors regressed markedly and most of them became undetectable, while tumors of other groups receiving normal lymphocytes or medium combined with irradiation ceased to regress soon after the treatment. This effect of IL was abolished by the treatment of IL with anti-Thy 1 antibody and complement, and was not observed against antigenically distinct syngeneic tumors (Meth-A). Concomitant transfer of spleen cells from mice bearing progressing tumors with IL partially impeded the effect of IL. These results suggest that specific immune T lymphocytes induce tumor regression when transferred after the whole body irradiation of the tumor-bearing mice. The effects of irradiation may be divided into two categories: the direct effect on tumor cells, and the indirect effect upon the activity of IL. (Author abstract) (30 Refs)

53. COOPERATIVE ROLE OF T LYMPHOCYTES AND MACROPHAGES IN ANTI-TUMOR ACTIVITY OF MICE PRETREATED WITH SCHIZOPHYLLAN (SPG).

Suzuki M, Arika T, Amemiya K, Fujiwara M
Central Res. Lab., Kaken Chemical Co., Ltd., Honkomagome, Bunkyo-ku, Tokyo 113, Japan
Jpn J Exp Med; 52(2):59-65 1982

Anti-tumor activity against Sarcoma-180 was studied in female jcl:ICR mice injected ip with schizophyllan (SPG), a glucan produced by Schizophyllum commune. Anti-tumor activity was transferrable into normal mice by lymph node cells of animals pretreated with SPG and lasted up to 60 days after SPG administration to donor mice. In vitro treatment of SPG-treated lymph node cells with anti-Thy-1.2 sera and complement abolished the anti-tumor activity. Spleen cells from SPG-treated mice induced anti-tumor activity up to 10 days, but lost effectiveness by 60 days. Delayed cutaneous hypersensitivity reaction with picryl chloride was enhanced in mice receiving lymph node cells form SPG-treated donor mice; such enhancement was not observed when spleen cells were used. In vivo treatment with inhibitors of macrophage function (trypan blue and carageenan) reduced the anti-tumor activity of SPG in injected mice and decreased the effectiveness of transferred spleen or lymph node cells. The anti-tumor activity in SPG-treated mice apparently derived both from activated macrophages and T-cells in the lymph node or spleen. The T-cells and macrophages may cooperate in each other's activation. (11 Refs)

54. ADOPTIVE CHEMOIMMUNOTHERAPY OF A SYNGENEIC MURINE LYMPHOMA WITH LONG-TERM LYMPHOID CELL LINES EXPANDED IN T CELL GROWTH FACTOR.

Eberlein TJ, Rosenstein M, Spiess P, Wesley R, Rosenberg SA
Surgery Branch, Div. Cancer Treatment, NCI, NIH, Bethesda, MD, 20205
Cancer Immunol Immunother; 13(1):5-13 1982

The cure of disseminated syngeneic FBL-3 lymphoma in female C57/BL/6 mice was attempted with the use of in vivo-immunized cells, in vitro-sensitized cells, whole lymphoid populations expanded in T cell growth factor (TCGF), and with cloned cytotoxic cells expanded in TCGF. In 3/3 experiments, 20/38 mice receiving cytoxan (CY) plus in vivo-immunized lymphoid cells were cured of tumor compared to 0/31 mice treated with CY plus normal lymphocytes. In vivo-immunized lymphocytes were resensitized to irradiated FBL-3 tumor in complete medium (CM) or lectin-free TCGF (LF-TCGF). In the CM group 41/50 animals were cured. In the LF-TCGF group 36/61 animals were cured. No significant difference was observed in the in vivo effects of cells in vitro sensitized (IVS) in CM or LF-TCGF. IVS cells were resensitized in vitro to irradiated FBL-3 tumor for 5 days. Simultaneously, normal C57BL/6 lymphocytes were co-cultured with normal C57BL/6 irradiated stimulators. Neither of these groups showed significant lysis of fresh FBL-3 tumor in an 18-hr 51Cr-release assay in six of eight experiments. Treatment of mice with CY plus immune lymphocytes sensitized to normal C57BL/6 stimulators and then expanded in LF-TCGF resulted in no increase in survival compared with CY alone. Treatment of mice with CY plus immune lymphocytes resensitized to FBL-3 tumor in vitro and expanded in LF-TCGF cured 7/27 animals and prolonged survival over that in all control groups. Treatment with CY plus normal nonimmune lymphocytes resensitized to normal C57BL/6 stimulators and expanded in LF-TCGF for 2.5 mo did not prolong survival compared with CY controls. CY plus immune lymphocytes sensitized to FBL-3 tumor and expanded continuously in LF-TCGF for 2.5 mo showed marked prolongation of survival and cured 5/9 mice. Implications of results for application of these techniques to other less antigenic tumors and human cancers are discussed. (49 Refs)

55. ANTITUMOR EFFECT OF POLYSACCHARIDE LENTINAN ON MH-134 ASCITES HEPATOMA IN C3H/HE MICE.

Moriyama M
Dept. Surgery, Okayama Univ. Medical Sch., Okayama 700, Japan
Acta Med Okayama; 36(1):49-60 1982

Lentinan inhibited the proliferation of MH-134 ascites hepatoma transplanted subcutaneously. The best result occured when 1 mg -2 mg/kg of lentinan was administered for 10 consecutive days from 8th day after tumor transplantation. Tumor proliferation was 33% inhibited as measured by the av tumor diameter. The av survival (days) when chemotherapy with mitomycin-C (MMC), 5-fluorouracil (5-FU) and Ara-C in combination with lentinan, was administered concurrently in the 2nd wk of the tumor transplantation was 29.2 days as compared to 20.5 days in the untreated group, 25.1 days in the group given lentinan alone, and 22.0 days in the group receiving chemotherapy alone. when lentinan was administered in combination with bacterial lipopolysaccharide (LPS), the group given lentinan for 5 consecutive days from the 3rd day after tumor transplantation and 30 ug LPS ip on the 13th day, had 70% inhibition of tumor as measured by the av tumor wt. The antitumor activity of lentinan was studied by following changes in macrophage migration inhibition activity (MI). In the untreated group, MI activity disappeared on the 14th day after tumor transplantation. In the group treated with lentinan, spleen cells had positive activity suggesting a restorative action of lentinan on the immune suppression accompanying tumor growth. (Author abstract) (25 Refs)

56. SUPPRESSION OF T AND B CELL DEPENDENT IMMUNE SYSTEMS IN CHICKEN.

Gupta SK, Kharole MU, Kalra DS
Dept. Veterinary Pathology, Haryana Agricultural Univ., Hissar 125 004, India
Indian J Exp Biol; 20(3):200-203 1982

A technique for the suppression of both T and B cells is described in White Leghorn chickens which could be used in the study of the role of components of the immune system in health and disease. T cell suppression (TX) in 54-day-old birds was accomplished by surgical removal of the thymus. On subsequent days, each chicken received 0.75 ml injections twice daily of whole serum prepared against chicken thymus. The adequacy of TX was determined by the graft vs host reaction in chicken embryos injected with 0.2 ml of test blood. B cell suppression (BX) was accomplished by treatment of 50 chicks with Endoxan (CY: 4 mg by the intraabdominal route) daily for 4 days starting on day 2 of age. This was followed by treatment of each CY-treated chick with 0.75 ml inoculations of antibursal sera on days 7 and 8. The adequacy of the Bursa dependent immune system of chickens was evaluated by three criteria: examination of the Bursa of Fabricius (BF) in BX and normal chicks; similar microscopic examination of the BF; and suppression of antibodies. The latter test involved use of chicks vaccinated with herpes virus of turkeys (HVT) at 11 days and challenge with Marek's disease virus (MDV) on day 42 of age. The ability of BX chicks to produce antibodies against HVT and MDV was tested by agar gel precipitation. These studies indicated that functional suppression of both B and T cells had been achieved. (14 Refs)

57. TUMOR BEARER T CELLS INTERACT WITH ANTIGEN STIMULATED AUXILIARY T CELLS TO SUPPRESS BCG POTENTIATED ANTITUMOR RESPONSES (MEETING ABSTRACT).

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Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Assoc Cancer Res; 23:960 1982

T cells (Ts) from BALB/c mice bearing syngeneic Meth A tumors for 6 days can adoptively suppress the efferent phase of delayed-type hypersensitivity (DTH) in BCG primed and unprimed recipients which have been sensitized with syngeneic irradiated tumor cells but do not affect the augmented DTH response obtained when recipients have been inoculated with cyclophosphamide (CY) 2 days prior to sensitization. Their failure to suppress the CY augmented DTH response was not due to transfer of inadequate numbers of cells, for doses as high as 4x10(8) spleen cells were without effect. This implied that Ts interact with CY-sensitive auxiliary cells to suppress DTH. Reconstitution of CY-treated immune recipients with selected spleen populations prior to adoptive transfer of Ts revealed that auxiliary efferent-phase suppressor cells are present in immune but not normal spleen populations in both BCG primed and unprimed hosts. These auxiliary cells are Thy+, Lyt 1-23+ and bear I-J determinants. Their activity is not influenced by B cell depletion. They are sensitive to cortisone and irradiation with 900 or more rads. They are not actively dividing as evidenced by their insensitivity to Vinblastine, nor do they adhere to Sephadex G-10. These last two characteristics and their cortisone sensitivity distinguish them from Ts. Elucidation of the mechanism(s) which render an immune response invulnerable to suppressor T cells has obvious practical value for clinical immunotherapy. (no Refs)

58. DYNAMIC CHANGES OF T-CELL AND NON-T-CELL IMMUNITY DURING MCA-38 TUMOR PROGRESSION (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:1023 1982

Studies with the Winn test have indicated that neutralization of chemically induced tumors requires cooperation between donor T-cells and recipient non-T-cells. The objective of this study was to determine if non-T-cell immunity is also present in the tumor bearing host. Spleen cells from normal C57B1/6J mice and mice bearing the chemically induced MCA-38 tumor were fractionated. T-cell (E) and non-T-cell fractions from normal and tumor bearing mice harvested 4,8,12,16,20 and 25 days post MCA-38 sensitization were admixed with MCA-38 tumor cells (T) at an E:T ratio of 50:1 and transferred to normal mice. The sensitized T-cell fraction could neutralize tumor growth (greater than 50%) between days 4 and 20 with maximal neutralization occurring on days 12 and 16. The sensitized non-T-cell fraction could neutralize tumor growth between days 8 and 16 with maximal neutralization occurring on day 12. Tumor neutralization with the sensitized T and non-T fractions was not observed with the B-16 melanoma tumor indicating that tumor cell neutralization in the MCA-38 system is immunologically specific. These results indicate that both T and non-T cell fractions can neutralize tumor growth but the temporal expression of anti-tumor immunity of these fractions markedly differs. (no Refs)

59. STUDIES ON THE INTERRELATION OF RESISTANCE AND IMMUNITY IN A MOUSE MODEL SYSTEM OF HERPES-SIMPLEX TYPE 2 INFECTION.

Armerding D

Immunology Dept., Sandoz Forschungsinstitut GmbH, Brunner Strasse 59, 1235 Vienna, Austria

Immunobiology; 161(5):415-428 1982

Intraperitoneal (ip) vaccination of mice with attenuated herpes simplex virus Type 2 (HSV 2) induced solid protection to ip infection with pathogenic virus within 2 days. Protection was non-virus-specific until Day 4 after sensitization but increased in specificity thereafter. Normal mice could be protected by adoptively transferred spleen cells, serum, and peritoneal fluid from donors vaccinated seven days before. Virus-specific effector cells induced in the spleen by in vivo ip sensitization with either live, pathogenic, or attenuated virus and tested in a cytotoxicity assay were exclusively B lymphocytes. No functional B cells, but natural killer (NK) cells, could be detected in the unseparated peritoneal exudate cell (PEC) population. Ability to generate HSV2 specific antibody responses did not correlate with natural resistance. (Author abstract) (40 Refs)

60. IMMUNOTOXICOLOGY STUDIES ON LEAD: EFFECTS OF EXPOSURE ON TUMOR GROWTH AND CELL-MEDIATED TUMOR IMMUNITY AFTER SYNGENEIC OR ALLOGENEIC STIMULATION.

Kerkvliet NI, Baecher-Steppan L
Sch. Veterinary Medicine, Oregon State Univ., Corvallis, OR, 97331
Immunopharmacology; 4(3):213-224 1982

Chronic exposure of C57Bl/6 mice to lead acetate in drinking water enhanced growth of primary Maloney sarcoma virus (MSV)-induced tumors. In a subsequent continued survival study, exposed mice showed a decrease in late-appearing progressive tumors. Cell-mediated cytotoxic response in spleen or lymph nodes of tumor-bearing mice was significantly augmented by lead exposure. Further studies in an allogeneic tumor model and studies of macrophages from lead-exposed mice suggest significant impairment of macrophage function by lead. (33 Refs)

61. DIFFERENCES IN SPLEEN SUPPRESSOR CELL CONTENT IN RATS WITH PROGRESSING AND REGRESSING TUMORS.

Hollingsworth MA, Evans DL
Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., 300 South Hawthorne Road, Winston-Salem, NC, 27103
JNCI; 69(1):53-58 1982

Young New Zealand Black rats (less than 35 wk old) developed progressively growing tumors when given injections of cells from a syngeneic 3-methylcholanthrene (MCA)-induced fibrosarcoma. Spontaneous tumor regression occurred in animals more than 10 mo of age. Compared to the responses of spleen cells from age-matched controls, spleen cells from rats in which tumor progression was present (progressor rats) showed decreased proliferative responses to concanavalin (Con A). phytohemagglutinin (PHA), and syngeneic MCA tumor cells. Spleen cells from rats in which the tumors had regressed (regressor rats), however, produced significant increases in proliferative responses when compared with the responses of spleen cells from age-matched controls and from progressor rats. Cell-mixing experiments implicated the presence of two spleen suppressor cell populations in progressor rats, one of which was not present in regressor rats. The unique suppressor cell found in progressor rats appeared to be specific for tumor cell-induced proliferative responses. Spleen cells from both progressor and regressor rats produced similar suppressive effects in the PHA and Con A responses of normal cells. (Author abstract) (30 Refs)

62. EFFECT OF T AND B CELL IMMUNOSUPPRESSION ON THE RELEASE OF MAREK'S DISEASE VIRUS FROM THE FEATHER FOLLICLES OF CHICKENS.

Gupta SK, Kharole MU, Kalra DS
Dept. Veterinary Pathology, Haryana Agricultural Univ., Hissar 125 004, India
Indian J Exp Biol; 20(2):179-180 1982

The release of Marek's disease virus (MDV) from feather follicles of Marek's disease infected chicks was delayed by 2 wk in chicks vaccinated with herpes virus of turkeys (HVT). T cell suppression (by thymus ablation and antithymus treatment) and B cell suppression (by injection of cyclophosphamide and anti-bursa serum treatment) had no significant effect on release of MDV in HVT vaccinated chickens. (12 Refs)

63. THE INCREASE OF A NORMALLY OCCURRING K CELL POPULATION DURING PROGRESSIVE TUMOR GROWTH IN MICE.

Gadol N, Saluk PH
Dept. Microbiology and Immunology, Hahnemann Medical Coll. and Hosp., 230 N. Broad St., Philadelphia, PA, 19102
Int Arch Allergy Appl Immunol; 69(2):127-133 1982

K cell activity of the spleen cells from normal and tumor-bearing mice was compared using an antibody-dependent cellular cytotoxicity assay. The K cell activity increased with progressive tumor growth (syngeneic) compared to the K cell activity of normal mice. The increase in K cell activity most likely reflected an increase in the numbers of K cells normally present in nontumor-bearing mice rather than the emergence of a distinct population of K cells induced by the growing tumor. (Author abstract) (30 Refs)

64. CHARACTERIZATION OF A MAJOR NATURAL KILLER ACTIVITY IN RAT LUNGS.

Nolibe D, Berel E, Masse R, Lafuma J
Commissariat a l'Energie atomique, Institut de Protection et de surete nucleaire, Boite postale 561, 92542 Montrouge, France
Biomedicine [Express]; 35(7/8):230-234 1981

A high level of antitumoral cytotoxicity was observed in the lymphoid population extracted by perfusion from lung capillaries. The in vitro cytotoxicity against tumor cells was demonstrated with the murine lymphoma YAC-1 cells or with the syngeneic P 77 rat lung fibrohistiocytoma cells. It was demonstrated that this cytotoxic activity had the characteristics of natural killer activity. At the same effector to target ratio the efficiency of this population was higher than in blood or spleen. Since the total number of lymphoid cells arrested in the capillary of the lungs is very high the lungs seemed an immunologically privileged site. A close relationship was observed between this activity in vitro and the rapid elimination in vivo of same tumor cells trapped in lungs (more than 99% after 24 hr). (Author abstract) (16 Refs)

65. PROTECTION OF NEONATAL MICE AGAINST HERPES SIMPLES VIRUS INFECTION: PROBABLE IN VIVO ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY.

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Univ. Texas, P.O. Box 20708, Houston, TX, 77025
J Immunol; 129(1):370-376 1982

Infant mice are extremely susceptible to fatal Herpes simplex virus (HSV) infection. They are unable to produce antibody to HSV, and their leukocytes cannot mediate antibody-dependent cellular cytotoxicity (ADCC) to HSV-infected cells. In order to avoid H-2-dependent effector mechanisms and instead analyze possible in vivo ADCC, a murine model employing adoptive transfer of antibody and human leukocytes was developed. Administration of either human immune globulin or leukocytes ip from HSV immune or nonimmune humans could not protect infant C57BL/6 mice from fatal HSV infection. In contrast, a combination of a subneutralizing dilution of globulin and leukocytes from nonimmune or immune human donors, given 1 day before inoculation, was highly protective against lethal HSV infection. The cells involved included lymphocytes or monocyte-macrophages. At least 5 x 10(6) viable leukocytes (or 1 x 10(6) monocyte-macrophages) and immune serum globulin concentrations as low as 10(-8) were protective. Infected cell monolayer adsorption and DEAE column fractionation demonstrated that the protection by globulin was due to specific antiviral IgG antibody. Protection was not seen in animals receiving virus before immune transfer. Protection did not involve synergistic viral neutralization by antibody and cells, as shown by in vitro experiments. Animals receiving globulin and cells, unlike normal infant mice, had circulating antiviral antibody and peritoneal leukocytes able to mediate ADCC to HSV-infected cells. This is the first in vivo evidence for the role of human ADCC. This model also allows for the in vivo evaluation of the ability of cells from immunocompromised humans to curb viral infection. (Author abstract) (72 Refs)

66. THE IMMUNE RESPONSE TO A CHEMICALLY INDUCED FIBROSARCOMA: A COMPARISON OF CYTOLYTIC T LYMPHOCYTE STIMULATION BY TRANSFORMED AND NON-TRANSFORMED FIBROBLASTS.

Bowlin TL, Proffitt MR
(c/o Proffitt) Dept. Biology, Cleveland State Univ., Cleveland, OH, 44115
Cancer Immunol Immunother; 13(1):30-37 1982

Cell-mediated immune response to a particular strain of 3-methylcholanthrene-transformed murine fibroblasts (MCA-C3H clone 15) was examined with emphasis on determining whether the cells, compared with non-transformed fibroblasts (C3H10T1/2), could stimulate the generation of syngeneic or allogeneic cytolytic effector spleen cells in vitro. When normal C3H/He spleen cells were co-cultured for 5 days with x-irradiated normal syngeneic fibroblasts, few effector cells capable of lysing either normal or tumor target fibroblasts were generated. Fibroblasts were unable to stimulate an allogeneic cell-mediated cytotoxicity (CMC) response and were very poor targets for C57BL/6 effector cells. Results indicated that tumor fibroblasts (TF) can be lysed by allogeneic effector cells when C3H/He spleen cells are used. TF expressed alloantigenic determinants similar to those found on the normal fibroblasts. Syngeneic C3H/He spleen cells proliferated in the presence of normal, but not tumor, C3H fibroblasts (x-irradiated 1,000 R) as measured by tritiated thymidine uptake. Data indicated that not only do syngeneic and allogeneic spleen cells fail to proliferate in the presence of TF, but even background levels of proliferation are inhibited. Addition of third-party TF to the sensitization phase of an allogeneic (C57 spleen x C3H normal fibroblasts) CMC assay inhibited the generation of T cells cytolytic for the normal C3H fibroblasts. Results of studies involving the use of indomethacin suggested that prostaglandins are not involved in MCA-C3H TF suppression of normal allogeneic cytolytic T cell generation. (29 Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

67. NATURAL KILLER ACTIVITY AGAINST RETROVIRUS INFECTED CELLS: DICHOTOMY IN NK SENSITIVITY OF INFECTED T AND B CELLS.

Dubey DP, Staunton D, Azocar J, Stux S, Essex M, Yunis EJ
Sidney Farber Cancer Inst., Harvard Medical Sch., Sch. Public Health, Boston, MA, 02115
Clin Immunol Immunopathol; 23(2):215-223 1982

Analysis of the natural killer cell activity against persistently FeLV-infected human T- and B-cell lines HSB-2, RPMI-8402, Raji, and RPMI-8392, and their uninfected counterparts, suggests that feline leukemia virus(FeLV) infection modifies NK sensitivity of T and B cells in different ways. In contrast to infected B cells, which demonstrated a dramatic increase in susceptibility to NK-mediated lysis relative to uninfected cells, infected T (HSB-2 and 8402) cells demonstrated a significant decrease. This pattern of lysis was independent of the NK assay duration. The resistance of NK-mediated cytotoxicity is not due to serum, nor to variation in virus replication in the host cells. This dichotomous response to retrovirus infection suggests different mechanisms of viral interaction leading to the development of specific malignancies through an immune surveillance escape mechanism. (Author abstract) (29 Refs)

68. BCG INDUCED MURINE PERITONEAL EXUDATE CELLS: CYTOTOXIC ACTIVITY AGAINST A SYNGENEIC BLADDER TUMOR CELL LINE.

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J Urol; 127(6):1225-1229 1982

Peritoneal exudate cells from mice after intraperitoneal injection of 10 mg of BCG demonstrated cytolytic activity in vitro against the syngeneic bladder tumor cell line MBT-2. The cytolytic effector cells are nonadherent, nonphagocytic and trypsin resistant. Moreover these cells are cyclophosphamide and hydrocortisone sensitive. It is suggested that an NK-like cell constitutes the major, if not all the population of effector cells in this reaction. (Author abstract) (33 Refs)

69. NATURAL KILLER CELLS INDUCED BY ACUTE AND CHRONIC TOXOPLASMA INFECTION.

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Cell Immunol; 69(2):330-346 1982

The recent interest in natural killer (NK) cells in immunosurveillance and the ability of infection with certain organisms to modulate NK activity led us to examine the influence of Toxoplasma gondii infection on mouse NK cells. Infection of BALB/c mice with 5 x 10(3) virulent Toxoplasma intraperitoneally (ip) resulted in significantly enhanced NK activity in peritoneal exudate cells (PC) and in spleen cells (SC). Intravenous (iv) and subcutaneous (sc) challenge of BALB/c mice with Toxoplasma also resulted in enhanced natural killer (NK) activity in PC and SC. In BALB/c mice, as well as in other strains (A/J, C57BL/6, C3H/HeJ, CeH/HeN, [A/J x C3H]F1), peak augmentation of PC and SC NK activity was observed 3 days following ip Toxoplasma challenge. Administration of silica to mice abolished Toxoplasma-induced NK cytotoxicity. BALB/c mice chronically infected with Toxoplasma had significantly higher endogenous NK activity than did controls in PC but not in SC. Chronically infected BALB/c mice boosted with virulent Toxoplasma ip exhibited significantly enhanced NK activity in PC but not in SC. Thus, acute and chronic infection with Toxoplasma modulates NK activity in addition to macrophage activation and thereby provides a system that should facilitate study of the relative contribution of NK cells and activated macrophages in resistance to tumor growth and spread. (Author abstract) (60 Refs)

70. MEDIATION OF CELLULAR IMMUNITY IN CANCER BY IMMUNE MODIFIERS.

Chirigos MA, Mastrangelo MJ, Mitchell M, Krim M
Viruses and Disease Modification Section, Div. Cancer Treatment, NCI, NIH, Bethesda, MD, 20205
Prog Cancer Res Ther; 190:1-275 1982

Among the 25 papers included in this volume are a number of studies on the characteristics of cytotoxicity against a variety of tumor cells (animal and human) by macrophages, natural killer (NK) cells and antibody dependent cellular toxicity (ADCC). Many of the papers have important implications for the possible role of these effector cell mechanisms as mediators of biological response modification. Other subjects treated include: the interrelationships of interferon and interferon inducers to enhance NK cell, and ADCC tumor-lytic effect on animal and human tumors, the relationship of prostaglandins and other immunoregulating agents on feedback inhibition mechanisms and suppressor cells which can modify the immune response. One chapter presents a study undertaken to directly investigate the mechanism(s) whereby cytosine arabinoside influences ADCC activity and Fc receptors. (564 Refs)

71. SUPPRESSION OF CELL-MEDIATED ANTITUMOR IMMUNITY BY COMPLETE FREUND'S ADJUVANT.

Koyama S, Yoshioka T, Sakita T
Dept. Internal Medicine, Inst. Clinical Medicine, Univ. Tsukuba, Ibaraki 305, Japan
Cancer Res; 42(8):3215-3219 1982

The effect of complete Freund's adjuvant (CFA), which is one of the strong immunoadjuvants, on the induction of either cytotoxic or suppressor T-cells against syngeneic tumors was investigated by an in vitro assay system. CFA did not show the apparent augmenting activity in the induction of cytotoxic T-cells against syngeneic tumors when it was administered ip to mice receiving sc inoculations of mitomycin C treated tumor cells. The treated animals failed to develop stronger resistance against the second inoculum of the same viable tumor cells. Furthermore, CFA had an effect on the induction of suppressor T-cells in tumor-bearing hosts in which suppressor T-cells had been readily activated. Suppressor T-cells developed in syngeneic tumor-bearing mice treated with CFA was tumor specific. Tumor growth was enhanced when CFA was administered to mice given sc inoculations of the homologous tumor. (Author abstract) (21 Refs)

72. EFFECT OF SPLENECTOMY ON THE PROGRESSION OF POSTOPERATIVE PULMONARY METASTASES OF THE 3LL TUMOR.

Ron Y, Gorelik E, Feldman M, Segal S
Dept. Cell Biology, Weizmann Inst. Science, Rehovot, 76100, Israel
Eur J Cancer Clin Oncol; 18(4):391-397 1982

Surgical excision of the local intrafootpad tumor of the 3LL lung carcinoma is followed by accelerated growth of its lung metastases. When, however, splenectomy was performed concomitantly with tumor excision, the acceleration of lung metastases was prevented. In cases where excision of the local tumor took place when it reached large sizes, concomitant splenectomy did not prevent the accelerated growth of the lung metastases. If, however, at these stages of tumor growth splenectomy was performed 3 days prior to the excision of the tumor, it did prevent the accelerated growth of metastases. Intrafootpad reinoculation of tumor cells following tumor excision and splenectomy caused further reduction in metastatic growth. The results suggest the existence of two possible distinct mechanisms which control metastatic growth: the local tumor might exert non-immunologically, an inhibitory effect on its lung metastases, and the spleen, possibly via suppressor lymphocytes, may suppress an immune effector activity against the tumor metastases, an activity which is manifested following splenectomy. (Author abstract) (21 Refs)

73. INHIBITION OF KILLER-TARGET CELL INTERACTION BY MONOCLONAL ANTI-LY-M11 ANTIBODY.

Tomonari K, Tada N, Kimura S, Hammerling U, Weksler ME
Dept. Medicine, Cornell Univ. Medical Coll., 1300 York Ave., New York, NY, 10021
Immunogenetics; 15(6):605-608 1982

Covering of Ly-m11 antigen sites with antibody on the target cell prevented partially recognition and lysis by cytotoxic T lymphocytes (CTL). The mechanism of inhibition was in principle different from the inhibition produced by anti-Lyt-2 antibody that acts on the CTL. It was suggested that anti-Ly-m11 binds to B2m on the target cell, and thus forms a structurally integral part of the H-2 antigen. (10 Refs)

74. PHORBOL ESTER TUMOR PROMOTER MODULATION OF ALLOANTIGEN-SPECIFIC T LYMPHOCYTE RESPONSES.

Andreotti PE
Div. Immunology, Duke Univ. Medical Center, Durham, NC, 27710
J Immunol; 129(1):91-96 1982

The phorbol diester tumor promoter phorbol 12-myristate 13-acetate (PMA) was studied for its effects on T lymphocyte activation in allogeneic human mixed lymphocyte cultures. Lymphocyte proliferation was significantly enhanced in cultures with PMA at concentrations greater than or equal to 12.5 ng/ml, and interferon-gamma production was synergistically increased in cultures with PMA at concentrations greater than or equal to 5 ng/ml. In contrast, the generation of HLA-specific cytotoxic lymphocyte activity was completely inhibited in cultures with PMA at concentrations greater than or equal to 5 ng/ml. Fluorescence-activated cell sorter analysis with OKT mouse monoclonal antibodies indicated these PMA effects on lymphocyte activation are associated with an increase in the number of activated OKT4-positive T lymphocytes. (Author abstract) (41 Refs)

75. STUDY OF ANTI-CANCER IMMUNOTHERAPY TOLERANCE IN MAN BY ENDOVENOUS INFUSION OF 5 MG OF THE RIO DE JANEIRO STRAIN OF BCG.

Morais de Sa CA, Da Cunha Gomes M, De Paiva Rebelo PA, Rodrigues MA, Miguez LA, De Oliveira CA, Fialho F
Clinica Medica da Escola de Medicina e Cirurgia, Universidade de Rio de Janeiro, Rio de Janeiro, Brazil
Rev Goiana Med; 27(1/2):79-93 1981

In these studies, 57 patients with a histopathological diagnosis of advanced malignant neoplasms of various types were treated with 5 mg of Rio de Janeiro strain BCG. Their tolerance of this regime is documented. Side-effects were transitory in the majority of cases, disappearing spontaneously or by symptomatic treatment. Liver function tests were normal. Radionuclide imaging of the liver was done 30 to 40 days after immunotherapy. There was some damage to the hepatic parenchyma, in some cases areas of necrosis and biopsies were performed. Repeat radionuclide imaging showed later recovery from this damage. Endovenous administration offers the advantage of direct access by BCG to the tumor and quick stimulation of macrophages and lymphocytes. The dose of 5 mg was not repeated except in four cases because of the risk of immunosuppression. This treatment is best tolerated when accompanied by antipyretic and antiemetic therapy for a minimum of 6 hr following immunotherapy. (18 Refs) (In POR)

76. IMMUNOSUPRESSION BY HYPOXIC CELL RADIOSENSITIZERS: A PHENOMENON OF POTENTIAL CLINICAL IMPORTANCE.

Rockwell S, Kapp DS
Dept. Therapeutic Radiology, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510
Int J Radiat Oncol Biol Phys; 8(6):1071-1073 1982

Inhibition of cell-mediated immune responses induced by nitroimidazoles may be of clinical significance. Immunosupression by azathioprine is thought to result from the alkylating activities of the imidazole ring of 5-mercapto-1-methyl-4-nitroimidazole. Suppression of cell-mediated immunity could be a factor of clinical importance in a wide range of human malignancies, including lymphomas, lung carcinomas, and gynecologic cancers. A spectrum of different tests may be necessary to define completely the immunologic effects of each radiosensitizer. (32 Refs)

77. PHARMACOLOGICAL AND TOXICOLOGICAL STUDIES OF A NEW ANTITUMOR POLYSACCHARIDE, SCHIZOPHYLLAN.

Matsuo T, Arika T, Mitani M, Komatsu N
(c/o Komatsu) Dept. Bacteriology, Sch. Medicine, Showa Univ., 1-5-8 Hatanodai, Shinagawa-ku, Tokyo, Japan
Arzneim Forsch; 32(6):647-656 1982

Antitumor effect against syngeneic or allogenic tumor and biological response modifying activities of schizophyllan (SPG, a beta-1,3-D-glucan with a beta-1,6 linked D-glucose residue isolated from Schizophyllum commune Fries) were investigated. SPG exhibited the significant antitumor effects against syngeneic murine tumors, adenocarcinoma 755 (C57BL/6 mice) and MM 46 mammary carcinoma (C3H/He mice) as well as sarcoma 180. Antitumor effect of SPG significantly diminished in mice neonatally thymectomized and treated with antithymus globulin. SPG markedly augmented the development of allogeneic cytotoxic lymphocytes in vivo, or in vitro. Thus, antitumor effect of SPG was considered to be due to the augmentation of host defense mechanism closely connected with the T-cell functions. SPG enhanced the carbon clearance rate, accumulated into the reticuloendothelial system (RES) and increased the serum lysozyme activity, showing the stimulation of RES. Moreover, the macrophages activated with SPG exhibited the increases of cellular enzyme activities and spreading in addition to the development of cytolytic activity against tumor cells. These results taken together with the loss of antitumor effect of SPG in mice treated with trypan blue show that the mode of antitumor effect is expressed by cytotoxic macrophages in addition to T-lymphocytes. The enhancing effects of SPG on natural killer cell activity and serological factors possibly related to its antitumor activity were also observed. In conclusion, the present results of the pharmacological and toxicological studies suggest that SPG is a safe and useful immunoadjuvant for cancer therapy. (Author abstract) (28 Refs)

78. ENRICHED NATURAL KILLING AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY IN LYMPHOCYTE POPULATIONS ADHERENT TO TUMOR CELL MONOLAYERS.

Jensen PJ, Koren HS
NCI-Frederick Cancer Res. Facility, P. O. Box B, Frederick, MD, 21701
Immunobiology; 161(5):494-506 1982

We have previously shown that human peripheral blood lymphocytes that do not adhere to natural killer (NK)-sensitive target cell monolayers are at least partially depleted of NK activity. To demonstrate directly that NK effector cells adhere to the monolayers, we have now recovered the adherent populations by treatment with ethylenediaminetetraacetic acid. When tested immediately after isolation, these adherent populations show NK activity that is intermediate between that of the nonadherent and control cells. When antibody-dependent cellular cytotoxicity is tested concomitantly, the adherent fractions are consistently found to be enriched relative to control, unfractionated lymphocytes. In further studies, control populations and fractions nonadherent and adherent to HSB monolayers are incubated overnight at 37 C and then tested for NK activity. We find that the adherent fractions are selectively enhanced in activity, causing the NK activity of the adherent fractions to exceed that of control populations. The possible involvement of interferon in the augmentation of NK activity is considered. (Author abstract) (34 Refs)

79. SUSCEPTIBILITY OF HUMAN LEUKAEMIAS TO CELL-MEDIATED CYTOTOXICITY BY INTERFERON-TREATED ALLOGENEIC LYMPHOCYTES.

Moore M, Taylor GM, White WJ
Paterson Laboratories, Christie Hosp. and Holt Radium Inst., Whithington, Manchester, England
Cancer Immunol Immunother; 13(1):56-61 1982

Susceptibility to spontaneous cell-mediated cytotoxicity (CMC) of 22 human leukemias (13 acute myeloid, 9 lymphoid) by exogenous interferon (IFN)-treated and untreated lymphocytes from 24 unrelated normal donors was determined in eight experiments. Each leukemic target cell was tested with effectors from a minimum of 3 and a max of 11 donors, in parallel with tests on the K562 erythroleukemia line. In one experiment, CMC on the leukemias was demonstrable in two (E77, E79) of the four tested, as judged by evidence of amplification of cytotoxicity by IFN-treated effectors, compared with untreated peripheral blood lymphocytes, and a dose-response relationship over three effector-to-target (E:T) ratios tested. Considerable variation in the level of IFN-induced amplification was observed against both the cell line (E:T ratio 20:1) and the fresh targets (E:T ratio 40:1). The widest differences between IFN-amplified killing (IAK) and unstimulated CMC were found on E72 (25%), E76 (29%), and E84 (31%) among the myeloid leukemias, and E77 (32%) and E79 (29%) among the lymphoid leukemias. However, the level of IAK on the leukemias was almost without exception lower than that on K562 cells. Only 1/22 leukemias gave positive CMC (greater than 10%) with one or more donor lymphocytes without IFN pretreatment, compared with 10 with IFN pretreatment. Out of the total of 116 effector:leukamia cell combinations tested, one was positive without IFN, as against 22 that were positive with IFN. Seven leukemias were susceptible to IAK by more than one donor. No correlation between susceptibility to IAK, the morphological type of leukemia, and the induction of remission in those patients was observed. (38 Refs)

80. EFFECT OF HUMAN FIBROBLAST INTERFERON ON NATURAL KILLER CELL ACTIVITY: STIMULATION IN VITRO AND INHIBITION IN VIVO.

Heidemann E, Reichmann U, Wilms K, Treuner J, Niethammer D
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Klin Wochenschr; 60(12):625-629 1982

This paper describes the influence of human fibroblast interferon (IFN-beta) on the cytotoxic activity of natural killer cells (NK) in vitro and in vivo using the blood of healthy donors and myeloma patients. IFN-beta stimulates NK activity against all target cells tested in vitro in a dose-dependent way up to 250% of pretreatment values. At higher IFN concentrations, stimulation returned to baseline values. Stimulation was most pronounced in the lowest lymphocyte to target cell ratio. 1-to 2-h preincubation of effector cells with IFN was enough to achieve maximal stimulation. The effector cells of IFN-treated myeloma-patients, or patients with herpes zoster, showed a clear reduction of toxicity against all cells tested during the first infusion, as compared to the pretreatment values. (Author abstract) (22 Refs)

81. CYTOTOXICITY OF TEMPORARILY ADHERENT HUMAN MONONUCLEAR BLOOD CELLS. 1. CYTOTOXIC ABILITIES OF CELLS AFTER DETACHMENT FROM CULTURE WELLS.

Eggen BM
Section Hematology and Immunology, Trondheim Regional Hosp., N-7000 Trondheim, Norway
Acta Pathol Microbiol Immunol Scand [C]; 90(3):123-128 1982

Monolayers of freshly isolated peripheral blood monocytes are contaminated with 5-10% non-monocytic cells. These cells detach during the first day of in vitro culture, concomitant with a disappearance of the strong cytostatic and cytolytic activity of freshly isolated monocytes. The detached cells, mostly non-monocytic cells, exerted cytostasis and cytolysis on the human natural killer (NK) sensitive cell line K-562. The lytic activity was sensitive to trypsin treatment. The kinetics of cytolysis was NK-like, with maximal 51Cr-release within 4-8 hr of co-culture, and with a high degree of methyl-3H-thymidine release during the first 24 hr of co-culture. It is suggested that these cells may be a loosely adherent subpopulation of mononuclear cells with NK-like properties. (Author abstract) (17 Refs)

82. EFFECT OF INTRAPERITONEAL (IP) AND INTRAVENOUS (IV) ADMINISTRATION OF MVE-2 ON ANTIBODY DEPENDENT CELLULAR CYTOTOXICITY (ADCC) OF REGIONAL ADHERENT CELL POPULATIONS IN MICE (MEETING ABSTRACT).

Richman S, Tatum K
Departments of Medicine and Pharmacology, University of Louisville, School of Medicine, Louisville, KY, 40292
Proc Am Assoc Cancer Res; 23:963 1982

MVE-2 is a 15,500 molecular weight fraction of maleic vinyl ether. It has antitumor activity in a number of animal models and has recently been introduced into clinical trials. In animal systems macrophage cytotoxicity is increased following administration of MVE and this is thought to be the mechanism of antitumor activity. Because ADCC to chicken red blood cells in part reflects adherent cell cytotoxic activity, we tested the hypothesis that IP and IV administration of MVE would stimulate the regionally exposed (peritoneal exudate cell-PEC and spleen) adherent cell populations. Plastic adherent phagocytic PEC and splenocytes from BALB/c mice were tested for their ADCC activity in a 4 hr chromium release assay 608 days following 25 mg/kg of MVE-2 administered IP or IV. Adherent cell populations were microscopically examined and individual cells scored as being 'large' or 'small' based on an arbitrary dividing line of less than or greater than 8u in diameter. Followng IP injection of MVE-2, ADCC fell from 64% to 21% at a 6:1 E:T (effector:target) ratio and from 56% to 11% at a 3:1 E:T ratio. The yield of adherent PEC/mouse increased 50% following MVE injection. The % of small cells rose from 29% (uninjected control) to 43% (MVE). In contrast to these data, the IV administration of MVE resulted in an increase in ADCC activity from 26% to 69% at a 2:1 E:T ratio. The yield of adherent cells/spleen increased 6 fold but cell size did not markedly change. It appears that IP administration of MVE results in a depression of adherent cell ADCC in the peritoneal cell population which is probably the result of the influx of new small cells. This is in contrast to the ADCC activity of spleen cells following IV injection and to the results of classic macrophage cytotoxicity. We conclude that the two assays reflect different mechanisms of activation. (no Refs)

83. SELECTIVE EFFECTS OF ADRIAMYCIN IN MURINE HOST DEFENSE SYSTEMS.

Ehrke MJ, Cohen SA, Mihich E
Dept. Experimental Therapeutics and Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY, 14263
Immunol Rev; 65:55-78 1982

Effects of adriamycin (ADM) on allogeneic cell mediated cytotoxic (CMC) and phagocytic response, modification of responses to syngeneic tumor, modulation of the humoral responses, and effects of ADM on natural killer (NK) activity are discussed. Effect of ADM on the response of C57B1/6 spleen cells against P815 mastocytoma was evaluated using a 4-hr 51Cr release assay at the end of the 'effector development' stage. Effector cells involved in the ADM-augmented cytotoxic activity after culture were shown to be associated with cells both adherent and non adherent to plastic, insensitive to addition of silica 24 hr prior to assay, and eliminated following addition of anti-Thy 1.2 plus complement. No difference in crystallizable fragment (Fc) dependent phagocytic activity was observed with uncultured spleen cells from untreated mice or mice treated with ADM 1 or 5 days prior to sacrifice. Results were consistent with the suggestion that the necrosis observed 1 day after treatment with ADM involved an immature monocyte population in the spleen. According to results ADM does not affect CMC responses by selectively interacting with T-helper or T-suppressor cells. Administration of ADM (5 mg/kg, iv) to mice 5 days prior to inoculation with P815 cells resulted in either no effect or augmentation of the CMC response depending upon dose of antigen or day of assay. ADM, in general, inhibited humoral responses and NK activity when tested under conditions which led to an augmented CMC. (68 Refs)

84. POTENTIATED IMMUNE RESPONSES AFTER ADMINISTRATION OF ACLACINOMYCIN.

Orbach-Arbouys S, Andrade-Mena CE, Berardet M, Mathe G
Hopital Paul-Brousse, Institut de Cancerologie et d'Immunogenetique, F-94804 Villejuif Cedex, France
Int Arch Allergy Appl Immunol; 68(2):117-121 1982

After the intraperitoneal injection of aclacinomycin into mice, a variety of immune responses were increased. The total plaque-forming spleen cell response to SRBC was higher in treated animals than in controls, in spite of an apparent cytotoxic effect on B cells. The aclacinomycin-sensitive cell is apparently a long-lived cell, surviving adult thymectomy. Delayed-type hypersensitivity reactions were also augmented in treated animals, particularly those bearing tumors. In adjuvant-treated mice, the injection of aclacinomycin augments the immune response still further. Such observations should be taken into account in the establishment of clinical protocols associating immunotherapy and chemotherapy. (Author abstract) (17 Refs)

85. REGULATION OF HUMAN NATURAL KILLING BY LEVAMISOLE.

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Div. Immunology (Box 3010), Duke Univ. Medical Center, Durham, NC, 27710
Cancer Immunol Immunother; 13(1):24-29 1982

Effect of levamisole (LE) on human natural killing (NK) activity was studied in vitro. LE at concentrations greater than 10(-4) M clearly inhibited NK activity. Peripheral blood leukocytes (PBL) were pretreated with LE for 18 hr, washed free of the reagent, and then tested for NK activity. PBL pretreated with LE at concentrations greater than 10(-4) M again showed decreased NK activity, even though LE was not present during the NK assay suggesting that LE inhibited NK by decreasing effector cell activity, without affecting target cell susceptibility. The susceptibility of K562 to killing by complete medium (CM)-treated PBL or LE-treated PBL was, however, unaffected by LE treatment. The kinetics of effector cell inactivation was assessed by preincubating several aliquots of the same PBL effector cell preparation for a total period of 16 hr. Results of the experiment showed that greater than 4 hr was required to inactivate NK effector cells, if the activity was subsequently tested in the absence of the drug. Presence of 10(-3) M LE throughout the entire culture period depressed PBL response to phytohemagglutinin (PHA) stimulation. A 19-hr pretreatment with a subsequent wash had no effect on the response to PHA, while NK activity was greatly suppressed by the treatment. PBL were pretreated with LE and cultured in CM. PBL preincubated with 10(-3) M LE for 8 hr showed suppressed NK activity, as expected, when tested immediately after the preincubation. When the inactivated effector cells were incubated further for an additional 16 hr, the activity recovered to near-normal level. Therefore, the inactivation was reversible. (31 Refs)

86. IMMUNE ALTERATIONS RELATED TO AGE AND MAMMARY TUMOR DETECTION IN C3H/BI MICE.

Dufer J, Benoist H, Bouchet C, Desplaces A, Saracino RT
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Bull Cancer (Paris); 69(2):143-148 1982

The immune status of C3H/Bi mouse, a strain characterized by its high incidence of spontaneous mammary tumors, has been evaluated before and after palpable tumor detection. Spleen cells were studied in vitro: phytohemagglutinin (PHA) stimulation and antibody dependent cellular cytotoxicity (ADCC). Immune responses against sheep red blood cells, lipopolysaccharide and oxazolone were evaluated in vivo. Three mice groups were defined: 2-4 mo old mice without tumor - at that age, tumor frequency was near zero; 5-6 mo old mice, without palpable tumor - in this group, tumor appearance was very near, since 8-9 mo old mice showed a tumor frequency of 90-95%; tumor-bearing mice, more than 5 mo old. As compared to 2-4 mo old mice, 5-6 mo old mice without tumor showed an enhanced PHA stimulation of splenocytes and a decreased ADCC response. In addition, in vivo immune response to sheep red blood cells was decreased whereas other responses were unchanged. On the other hand, immune responses of tumor bearing mice did not differ from those of 2-4 mo old mice, both in vivo and in vitro. These data suggest a variation of immunological parameters in C3H/Bi mice, both in terms of age and of spontaneous mammary tumor appearance. (Author abstract) (15 Refs) (In FRE)

87. MANIPULATION OF HOST DEFENCE MECHANISMS.

Aoki T, Urushizaki I, Tsubura E
No affiliation given
Excerpta Med Int Congr Ser (576): 281 pp., 1981.

The manipulation of host defense mechanisms is discussed with particular attention given to lentinan, a potent augmenting agent. Lentinan is reviewed with respect to its antitumor effect and tumor-recognition in mice, inhibition of suppressor cell activity in the murine immune reaction, treatment of drug-resistant pulmonary tuberculosis; immunomodulating activity, inhibitory effects on the tumorigenesis of adenovirus Type 12 in mice, resistance against vesicular stomatitis virus-encephalitis, Abelson virus-induced tumor, and trophoblastic tumor in mice; immunopotentiating activity; augmentation of natural cell-mediated cytotoxicity in mice, augmentation of natural killer cell activity, antitumor effect on transplanted ascites hepatoma-134 in C3H/He mice, antitumor effect in the mouse system, immunological characteristics as immune adjuvants, and Phase I and II studies. Other topics discussed include the immune response influence regions in the rat hypothalamus, distinct characteristics of IgG-Fc and IgM-Fc receptors in sensitivity to enzymes and modulation by interferon, humoral immunoregulation in cancer patients, an immunoregulatory mechanism implicated by the blocking factors in serum from pregnancy, natural killer activity in patients with lung cancer, a combination of regional chemotherapy and systemic immunotherapy for the treatment of inoperable gastric cancer, the importance of timing for combination immunotherapy, a possible parameter for classifying immunomodulators, and cellular interactions in vitro in a primary anti-tumor response. (376 Refs)

88. CELLULAR AND MOLECULAR MECHANISMS OF IMMUNOLOGIC TOLERANCE.

Hraba T, Hasek M
Inst. Molecular Genetics, Czechloslovak Acad. Sciences, 166 10 Prague 6, Czechoslovakia
Immunol Ser 16: 570 pp., 1981.

Active mechanisms of immune tolerance, mechanisms of immune reaction inhibition at the cellular level, cellular interactions in immunologic tolerance, transplantation tolerance, and biological role of immunologic tolerance are discussed. Cancer-related presentations include the following: immunosuppressive effect of cyclophosphamide on normal and plasmacytoma-bearing mice; specific, long-lasting inhibition of IgG antibody production induced by antigen and 5-azacytidine; clonal deletion and suppression in relation to mechanisms of cyclophosphamide-induced tolerance; immune mechanisms in antithymocyte serum-induced progressive growth of tumor allografts in mice; the role of immunological and genetic factors in the development of spontaneous regression of Rauscher leukemia in mice, and studies on the role of macrophages and polymorphonuclear WBC in chemical immunosuppression. (1379 Refs)

89. LYMPHOKINES: A FORUM FOR IMMUNOREGULATORY CELL PRODUCTS.

Pick E, Landy M
Dept. Human Microbiology, Sackler Sch. Medicine, Tel-Aviv Univ, Ramat-Aviv, Tel-Aviv, Israel
Lymphokines 2: 313 pp., 1981.

Lymphokine (LK) activities are discussed. A systematic screening for LK activities detectable in the supernatants of continuous lymphoid and myeloid cell lines is presented. Present knowledge of T-cell growth factor (TCCF) and prospects for future LK studies stemming from the discovery and rapidly expanding application of TCCF are considered. Other topics discussed include the following: the central role played by T- and B-cell growth factors in the primary antibody response in vitro, the immune response in vitro, the role of antigen-specific T-cell factors in both help and suppression, the role of soluble factors in macrophage-T-cell interaction, the mechanism of action of LK, the mechanism of action of WBC migration inhibitory factor, the biological universality of LK, cytokine-like mediators secreted by malignant cells, tumor necrosis factor, the design of a method for enumerating LK-secreting cells, and the significance of the presence of LK in the tissues of animals and humans. (852 Refs)

90. SENSITIVITY TO MACROPHAGE-MEDIATED CYTOSTASIS IS CELL CYCLE DEPENDENT.

Hamilton TA, Fishman M, Crawford G, Look AT
Div. Immunology, St. Jude Children's Res. Hosp., Memphis, TN, 38101
Cell Immunol; 69(2):363-373 1982

We have examined the sensitivity of proliferating lymphoid cells in different phases of the cell cycle to macrophage-mediated cytostatic activity. These studies evaluated the ability of target cells enriched in individual cell cycle phases to pass into the next phase during brief (2-6 hr) periods of coculture with activated or nonactivated peritoneal macrophages. Both normal (concanavalin A-stimulated spleen cells) and neoplastic (Gross virus-induced thymic lymphoma) cells were analyzed. Spleen cells or lymphoma cells were first separated by centrifugal elutriation into populations highly enriched for G1, S, or G2/M phases of the cell cycle and cultured in the presence of nonactivated or activated macrophages for periods of 2, 4, or 6 hr. The cellular DNA content of recovered nonadherent target cells was then analyzed by flow cytometry after staining with propidium iodide. Macrophage contamination of target cell populations was insignificant under these conditions. Nonactivated macrophages did not affect target cell cycle traverse when compared with target cells cultured alone. Activated macrophage mediated cytostatic activity resulted in complete block of the transition of cells in G1 phase into S phase and of the further accumulation of DNA by cells in early S phase. Cells already in mid to late S phase were able to continue DNA replication at rates nearly equivalent to control cells. There was no inhibition of the passage of cells through G2 or mitosis. These effects were seen as early as 2 hr of macrophage-target cell coculture and both normal and neoplastic cells exhibited identical patterns of cell cycle phase sensitivity. (Author abstract) (21 Refs)

91. ABNORMAL EXPRESSION OF HISTOCOMPATIBILITY ANTIGENS ON CANCER CELLS.

Parmiani G, Pierotti MA, Colombo MP, Carbone G
Div. Experimental Oncology B, Istituto Nazionale Tumori, via Venezian 1, I-20133 Milan, Italy
Bull Cancer (Paris); 69(2):186-193 1982

Quantitative and qualitative alterations in the expression of the MHC products on experimental and human neoplastic cells are briefly reviewed. These alterations may influence the recognition and the immune response of cytotoxic T lymphocytes to tumor cells leading to an impairment of the host's defense against cancer. As an example, alteration of glycosylated prosthetic group of MHC products may occur spontaneously in tumor cells. The possibility that an artificially induced modification of glycosylated groups of H-2 antigens may influence a T cell-mediated tumor destruction was evaluated with the MBL2 lymphoma. It was found that a lower killing of the MBL2 cells by syngeneic, but not by alloimmune, T lymphocytes occurred when these targets were treated with tunicamycin, an inhibitor of glycosylation. The possibility of expression of extra H-2 or non-H-2 antigens on cancer cells has been exploited for antitumor therapy of a murine lymphoma, and in vivo and in vitro data are summarized showing the prevention of the growth of a syngeneic lymphoma in BALB/c mice immunized with normal allogenic cells. (Author abstract) (32 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

92. IN VIVO MACROPHAGE-MEDIATED TUMOR CYTOTOXICITY IN THE MOUSE.

Cameron DJ
Dept. Surgery, Medical Univ. South Carolina, Charleston, SC, 29425
Immunol Lett; 4(6):321-325 1982

Immunological activity of mouse peritoneal macrophages was studied in vivo in the presence and absence of lipopolysaccharide (LPS). LPS-activated macrophages acquired enhanced cytotoxicity for the DBA/2 mastocytoma (P815) cells at an effector:target ratio (ETR) of 25:1. The suppressive activity of control macrophages, LPS-activated macrophages, and dead control macrophages was compared with that of the animals receiving no macrophage treatments. No difference in tumor size could be demonstrated in any of the five groups of DBA/2 mice, 12 days after injection of the P815 cells. By day 17, the tumors in the mice treated with either control or activated macrophages at a 20:1 ratio had decreased in size. When the mice were injected with control or activated macrophages at the lower ETR of 10:1, the tumors increased slightly in size or remained the same as when measured on day 12. The mean survival time for the animals treated with LPS-activated macrophages at ETR of 20:1 (32 +-3.9 days), or control macrophages at ERT of 10:1 (30.7 +-2.96), or 20:1 (31.8 +-3.7 days) was longer than that for untreated control animals (21.2 +-2.2 days), whereas the mice treated with LPS-activated macrophages at ERT 10:1 (24.2 +-2.94 days) did not differ significantly from controls. Results showed that tumor cell growth can be slowed down in vivo when either LPS-activated or non-activated macrophages are injected into the site of the tumor mass. More LPS-activated macrophages than non-activated macrophages are required to inhibit tumor growth. (20 Refs)

93. IN VIVO SUPPRESSION OF SYNGENEIC MURINE FIBROSARCOMA BY MACROPHAGES AND LYMPHOCYTES.

Gupta N, Aikat BK, Sehgal S
Dept. Immunopathology, Postgraduate Inst. Medical Education and Res., Chandigarh 160012, India
Indian J Med Res; 75:583-589 1982

Various combinations of macrophages and lymphocytes, both specifically sensitized and non-sensitized, were given subcutaneously admixed with methylcholanthrene-induced fibrosarcoma cells in C-57 mice. Sensitized macrophages significantly suppressed tumor growth, reduced the mortality and prolonged life span. Tumor was found to regress in 43% mice. There was a marked suppression of tumor growth in groups of mice receiving sensitized lymphocytes, sensitized macrophages and normal lymphocytes along with tumor inoculum, whereas the combination of normal macrophages and normal lymphocytes was found to be ineffective in controlling tumor growth. Although sensitized macrophages plus sensitized lymphocytes along with tumor inoculum suppressed tumor growth, delayed its appearance, reduced mortality and significantly prolonged the life span, the effect was much less in extent than with sensitized macrophages alone. Thus, sensitized macrophages alone were found to be most effective in suppressing tumor growth, as compared to other combinations. (Author abstract) (16 Refs)

94. HOMOGENEOUS POPULATIONS OF MACROPHAGES FROM HISTIOCYTIC LYMPHOMA PATIENTS AS A SOURCE OF MACROPHAGE SUBPOPULATIONS WHICH DIFFER IN IMMUNOREGULATORY PROPERTIES.

Lavie G, Shoenfeld Y, Shaklai M, Aderka D, Pick AI, Pinkhas J
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Cancer; 50(1):69-77 1982

The existence of subpopulations of macrophages which express a variety of regulatory activities of other branches of the immune system is suggested in a comparative study of a human macrophage long term culture ZI and a macrophage cell line DAB-1. Both cell cultures were derived from pleural effusions of patients with diffuse histiocytic lymphoma. DAB-1 cells were found to secrete factors which strongly suppress the response of normal T and B lymphocytes to the mitogens PHA, Con-A and pokeweed mitogen (PWM) (by 96-98%) and to stimulate the cytotoxic activity of NK cells. ZI cells secrete factors which have a mild inhibitory effect on the response of lymphocytes to the T-cell mitogens PHA and Con-A and a stimulatory effect on the response to PWM, whereas very little effect could be detected on the activity of NK cells. While DAB-1 cells form large clusters during growth in culture, and are capable of inducing the formation of lymphocyte rosettes around the tumor cells, ZI cells grow as a homogeneous monolayer and could not be shown to form such rosettes. The differences in the behavior of the two cell populations suggest that the malignant transformation may have affected different subsets of macrophages in each case. Cells from histiocytic lymphoma patients may therefore be a source for homogeneous subpopulations of macrophages and their isolation and propagation in culture is one approach by which such subsets can be defined characterized and classified. The biological characterization of macrophage subsets may also be of clinical importance since a transformed subset with broad suppressor activities may lead to a violent and rapidly deteriorating course of disease, as was in the case of the patient from whom the DAB-1 cell line was derived. (Author abstract) (31 Refs)

95. CHANGES IN MACROPHAGES AND THEIR FUNCTIONS WITH AGING IN C57BL/6J, AKR/J, AND SJL/J MICE.

Wustrow TP, Denny TN, Fernandes G, Good RA
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Cell Immunol; 69(2):227-234 1982

Changes in phagocytosis, chemotaxis, and nonspecific esterase staining of peritoneal exudate mononuclear cells occurred with aging in B6, AKR/J, and SJL/J mice. Different patterns of change with aging were observed with each of these three parameters in each of the strains. In the long-lived B6 mice, a progressive increase with aging in all three parameters was seen. In AKR/J mice, progressive increase in phagocytosis and nonspecific esterase staining was observed but a decline of chemotaxis occurred with aging. In SJL/J mice, all three parameters were very low early in life and each showed a significant increment upon reaching the age when the characteristic malignant lymphoreticular disease occurs. (Author abstract) (39 Refs)

96. DERIVATION OF MACROPHAGE-LIKE LINES FROM THE PRE-B LYMPHOMA ABLS 8.1 USING 5-AZACYTIDINE.

Boyd AW, Schrader JW
Walter and Eliza Hall Inst. Medical Res., Post Office, Royal Melbourne Hosp., Melbourne, Victoria 3050, Australia
Nature; 297(5868):691-693 1982

Cloned ABLS 8.1 cells were cultured in the presence of various concentrations of 5-azacytidine (AC). Cells that survived culture with 1 uM AC were cloned with culture medium containing 2-mercaptoethanol (ME). Seven of 16 cell lines showed characteristics different from the parental line. A second series of variant lines was obtained without the use of ME. Both sets of cell lines have been re-cloned and have remained stable for over 3 mo of continuous culture. The granules and vacuoles present in these cells give them the superficial appearance of macrophages. A number of tests were performed on the derived and parent cells which indicated the derived cells possessed characteristic of macrophage cell lines. The most impressive test was phagocytosis of opsinized RBC which was not seen in control ABLS 8.1 cells and seems to be a unique property of macrophages. Other supporting evidence was the presence of esterase-positive granules and the presence on many of the cells of an antigen detected by the macrophage-specific monoclonal antibody (Mac-1). It is concluded that the demethylating drug AC has induced heritable morphological and functional changes in the pre-B-cell line ABLS 8.1 characterized by expression of macrophage-like features. (24 Refs)

97. EFFECTS OF PHORBOL MYRISTATE ACETATE AND A LYMPHOKINE ON CYCLIC 3':5'-GUANOSINE MONOPHOSPHATE LEVELS AND PROLIFERATION OF MACROPHAGES.

Hadden EM, Sadlik JR, Coffey RG, Hadden JW
Dept. Pharmacology, Univ. South Florida Medical Center, Tampa, FL, 66312
Cancer Res; 42(8):3064-3069 1982

The tumor promoter phorbol myristate acetate (PMA) was compared to a lymphokine macrophage mitogenic factor (MMF) for its ability to induce replication of guinea pig peritoneal and alveolar macrophages. Like MMF, PMA induces DNA synthesis of both cell populations with peak thymidine incorporation at 72 hr of culture. Optimal concentrations of PMA for the peritoneal and alveolar cells were 1.6 x 10(-7) and 1.6 x 10(-9) M, respectively. the magnitude of the effect is slightly less than MMF but greater than that of phytohemagglutinin or concanavalin A. Indomethacin added to inhibit prostaglandin synthesis potentiates the effects of MMF but has little effect on the actions of PMA and the other mitogens. Potentiation by indomethacin of the effects of PMA on the peritoneal cell was observed only at the suboptimal concentration of PMA (1.6 x 10(-8) M). By adherence criteria and density gradient fractionation, the cell responding to PMA is confirmed to be the macrophage. Cell counts and nuclear radioautography confirm that replication in this system is reasonably well reflected by thymidine incorporation. The effects of PMA and its analogs as macrophage mitogens correlate with their tumor-promoting effects. Both PMA and MMF induce early increases in peritoneal macrophage levels of cyclic 3':5'-guanosine monophosphate without changes in the levels of cyclic 3':5'-adenosine monophosphate. These studies indicate that PMA offers a useful probe of macrophage function. (Author abstract) (41 Refs)

98. EFFECTS OF CONDITIONED MEDIUM FROM NON-DIFFERENTIATING OR DIFFERENTIATED MOUSE MYELOID LEUKEMIA CELLS ON FORMATION OF MACROPHAGE-GRANULOCYTE COLONIES OF NORMAL MOUSE BONE MARROW CELLS.

Okabe-Kado J, Honma Y, Hayashi M, Hozumi M
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Gan; 73(3):398-402 1982

The effects of conditioned media (CM) of various clones of mouse myeloid leukemia cells (Ml) on colony formation of normal mouse bone marrow cells were examined under various conditions. The CM of sensitive Ml cells, which could be induced to differentiate into macrophage-like and granulocyte-like cells by various factors stimulating the differentiation (D-factor), slightly inhibited colony formation of normal bone marrow cells by colony stimulating factor (GM-CSF). The CM of resistant Ml cells, which were resistant to the induction of differentiation even with high concentrations of the D-factor, significantly inhibited the colony formation of bone marrow cells by GM-CSF. The inhibitory activity of the CM from resistant cells decreased on treatment of the cells with a low concentration of actinomycin D, which could sensitize the resistant cells to induction of differentiation. The CM of differentiated sensitive Ml cells induced by dexamethasone stimulated the colony formation of bone marrow cells without exogenously added GM-CSF. Most of the GM-CSF activity in the CM was separated from the D-factor of Ml cells by Sephadex G-75 gel filtration. (Author abstract) (19 Refs)

99. REPLICATION OF PLURIPOTENT STEM CELLS IN GRANULOCYTE/MACROPHAGE COLONIES DEVELOPED IN METHYLCELLULOSE CULTURE OF MOUSE BONE MARROW CELLS.

Miyanomae T, Tsurusawa M, Mori KJ, Mikawa H, Ito Y
Dept. Microbiology, Pediatrics, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
Gan; 73(3):408-412 1982

The existence of pluripotent hemopoietic stem cells in granulocyte/macrophage colonies was demonstrated in a culture of mouse bone marrow cells in semi-solid methylcellulose with spleen conditioned medium as colony-stimulating activity. When fresh growth medium containing the conditioned medium was supplemented to 1-wk culture, the number of cells per colony increased significantly in the next wk. The number of pluripotent stem cells also increased by a factor of 12 or more in the 2nd wk of the culture. The number of cell divisions in such a culture was calculated as 12-15 in 2 wk. These results indicate that some of the granulocyte/macrophage colonies are derived from pluripotent stem cells, and that the stem cells can undergo three to five self-replications in such semi-solid culture. (Author abstract) (16 Refs)

100. AGONIST-ANTAGONIST INTERACTIONS OF PHORBOL ESTERS IN MACROPHAGES (MEETING ABSTRACT).

Sturm RJ, Smith BM, Laskin DL, Lane RL, Harris LS, Lawrence W, Carchman RA
Department of Pharmacology, The Medical College of Virginia, Richmond, VA, 23298
Proc Am Assoc Cancer Res; 23:397 1982

Radioligand-receptor studies of the tumor promoter (TP) receptor on mouse peritoneal macrophages strengthens the relevancy of this interaction in modifying macrophage function. We have been able to identify the presence of a high affinity binding site (KD-50nM) for biologically active phorbol esters on the macrophage using 3H-phorbol-12,13-dibutyrate (PDBu) as the radioligand. The structure-activity relationship and the relative potency for 3H-PDBu displacement by various phorbol ester derivatives is the same as that obtained for these agents acting as macrophage chemoattractants. A comparison of the IC50 values of various derivatives for radioligand displacement with their EC50 values in the blind well Boyden chamber chemotaxis assay indicates there is an approximate one-to-one relationship between these two parameters. A phorbol derivative of particular interest to us is phorbol-12,13-diacetate (PDA). Though biologically inactive as a TP, PDA inhibits binding of 3H-PDBu (IC50-4uM). We also report that PDA inhibits macrophage chemotaxis (IC50-0.4 uM) to active phorbol ester derivatives while exhibiting no significant activity as a chemoattractant. Our findings indicate that phorbol ester induced chemotaxis in the macrophage is mediated by the high affinity tumor promoter receptor found on these cells. In addition, a comparison of the activity of PDA in these linked processes indicates that PDA is a receptor and biological antagonist of the phorbol ester agonists. (no Refs)

101. RECRUITMENT OF MACROPHAGES IN EXPERIMENTAL METASTASES (MEETING ABSTRACT).

Bugelski PJ, Poste G
Smith Kline and French Laboratories, Philadelphia, PA, 19101
Proc Am Assoc Cancer Res; 23:1004 1982

A new histochemical method has been developed to identify intratumoral macrophages and to monitor recruitment of macrophages into tumors and individual metastases. Macrophages are identified by their ability to phagocytize colloidal iron hydroxide and lanthanum chloride which are detected by hydrogen peroxide oxidation and cleavage of phosphate esters, respectively. The method is sensitive and provides permanent preparations from paraffin sections. Tumor-bearing mice are first injected iv with colloidal iron. Uptake of this material by intratumoral macrophages serves as a stable marker to identify macrophages present at the time of the first injection. Five, 10 or 15 days later the same mice are injected iv with lanthanum chloride. Animals are sacrificed 24 or 48 hours later, tumor-bearing tissues excised and fixed in formalin, and serial sections stained for either iron (blue reaction product) or lanthanum (magenta reaction product). The numbers of macrophages containing iron or lanthanum is then counted to provide an index of macrophage recruitment into tumor tissue. Application of this method to study macrophage behavior in lung metastases produced by the B16 melanoma in C57BL/6 mice revealed marked heterogeneity in both content and recruitment of macrophages into individual metastases within the same animal. (no Refs)

102. KINETICS OF ACTIVATION OF MACROPHAGES INDUCED BY DIMETHYLDIOCTADECYLAMMONIUM BROMIDE (DDA) (MEETING ABSTRACT).

Prager MD, Baechtel FS, Farmer JL, Gordon WC, Mauldin S, Steinberg J, Vanderzee J
University of Texas Health Science Center, Dallas, TX, 75235
Proc Am Assoc Cancer Res; 23:1033 1982

With tumor associated antigen (Ag), DDA stimulates murine anti-tumor responses in immunoprophylaxis and chemoimmunotherapy protocols. DDA effects are mediated by at least two processes: 1) complexing with Ag so as to present modified Ag to the immune system, and 2) macrophage activation as judged by a variety of parameters. The kinetics of parameter alteration for murine peritoneal macrophages following ip DDA injection has been investigated. Enhanced Fc receptor activity was observed day 1 after DDA and remained elevated through day 4. Peroxidase (cytochemical) was barely detectable on day 0, became strong on day 2, and dropped to pre-injection levels on day 4. The lysosomal enzymes beta-glucuronidase (betaG) and acid phosphatase (AP) were increased on day 2, peaked on day 3, and gradually declined over the next week. The maximum increase for betaG and AP was 3 and 12-fold/cell, respectively. Although betaG exhibited no increase in specific activity, that for AP increased 5-fold, indicating specific induction. The cytosolic enzyme lactic dehydrogenase presented a pattern like that of betaG. The effect of DDA induced macrophages on growth of one mouse and 2 human leukemic cell lines has been evaluated by cell enumeration. Relative to resident macrophages, day 4 DDA induced cells inhibited growth, but the leukemic cells exhibited variable sensitivity to macrophage attack. It is clear that these parameters by which macrophage activation is judged follow quite different kinetics. (no Refs)

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY

103. DISTINCT SIGNALS FOR ANTIBODY-DEPENDENT AND NONSPECIFIC KILLING OF TUMOR TARGETS MEDIATED BY MACROPHAGES.

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J Immunol; 129(1):427-432 1982

Conditions influencing the generation of antibody-dependent cellular cytotoxicity (ADCC) and several types of nonspecific tumor cell killing by macrophages were compared. Resident mouse peritoneal macrophages and several macrophage cell lines spontaneously display very low levels of ADCC to lymphoma targets. However, ADCC could be greatly stimulated in these macrophage populations by several days of culture with lipopolysaccharide (LPS), tumor promoter phorbol myristic acetate (PMA), and lymphokine (LK) preparations. Fibroblast L cell-conditioned medium (L-CM), a source of activities required for in vitro macrophage colony formation, also augmented ADCC. Two days of preincubation was optimal for stimulation of this cytotoxic activity. In contrast to these results, pretreatment of macrophages with any of the agents inhibitor tumor toxicity induced by nonspecific activating drugs present during the assay. This inverse relation between ADCC and nonspecific killing after pretreatment was obtained with peritoneal cells and two cloned macrophage cell lines. Thus, although the same cell or cell type can mediate both types of killing, the two mechanisms seem to be mediated by distinct states of a macrophage. The ADCC-stimulating agents, LPS, LK, and L-CM, probably have a common pathway of activation, because dexamethasone at 10(-6) M inhibited their effect. The factors in the LK and L-CM that stimulate ADCC are distinct from LPS, because the endogenous activities were inactivated by boiling. The activities are also separate from interleukin 2 and myeloid colony-stimulating factor purified from L-CM, CSF-1, had no effect on macrophage tumoricidal activity. ADCC-stimulating activity was not the same as macrophage-activating factor for nonspecific killing of fibrosarcoma targets, because the latter is not found in L-CM. It is concluded that macrophage ADCC and nonspecific cytotoxicity may be regulated by different endogenous signal and may represent different states of stimulated macrophages. (Author abstract) (41 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

104. A MONOCLONAL ANTIBODY (MMA) THAT IDENTIFIES A DIFFERENTIATION ANTIGEN ON HUMAN MYELOMONOCYTIC CELLS.

Hanjan SN, Kearney JF, Cooper MD
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Clin Immunol Immunopathol; 23(2):172-188 1982

A monoclonal IgMkappa antibody (MMA) was produced against the human histocytic cell line, U-937. This antibody reacted by indirect immunofluorescence and complement-mediated lysis with adherent mononuclear cells and granulocytes. MMA was unreactive with circulating T and B cells, erythrocytes, and platelets. Depletion of MMA+ cells from blood mononuclear cell populations significantly reduced the reactivity of these cells to antigens and mitogens. The lymphoproliferative responses were restored by addition of 10% MMA+ cells. MMA is expressed by some T-cell lines (HSB-2, MOLT-3, MOLT-4) and mitogen-activated T cells, but not by B-cell lines or activated B cells. Studies using double immunofluorescence showed that 80% of activated T4+ and 10% of T8+ cells expressed MMA. The antigen is present on precursors of in vitro granulopoietic colony-forming cells. Malignant cells from patients with both acute and chronic myeloid leukemias express this antigen. The MMA antibody thus defines a unique differentiation antigen present on human myeloid cells, their precursors, and a subpopulation of activated T cells. (Author abstract) (45 Refs)

105. ENRICHMENT OF COUNTERPART CENTRIFUGAL ELUTRIATION OF HUMAN LYMPHOCYTES CYTOTOXIC TO HUMAN TUMOUR CELLS.

Yasaka T, Wells RJ, Mantich NM, Boxer LA, Baehner RL
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Immunology; 46(3):613-617 1982

The enriched fractions of cytotoxic cells responsible for natural killer (NK) activity against both human sarcoma and neuroblastoma (LA-N2) cell lines were readily obtained by countercurrent centrifugal elutriation (CCE). The NK cells were obtained in the larger lymphocyte fractions (fraction 6 +-1), having a mean cell vol of 180 u3. The cytotoxic-enriched fraction contained 51% large lymphocytes having cytoplasmic granules. On the other hand, monocytes were purified to greater than 90% and isolated in another fraction (final fraction) and these cells had the lowest NK activity against both human tumor cell lines. However, compared with the lymphocyte fractions, small and large monocytes displayed greater antibody-dependent cellular cytotoxicity (ADCC) activity against human B erythrocytes. These results indicate that NK found to have activity against both tumor cell lines were large lymphocytes, not small monocytes. Thus, countercurrent centrifugal elutriation (CCE) can provide a sensitive method to obtain enriched fractions of large lymphocytes containing tumoricidal activity against human sarcoma and neuroblastoma cell lines. (Author abstract) (10 Refs)

106. CELL COMPETENCE FOR INDUCTION OF DIFFERENTIATION BY INSULIN AND OTHER COMPOUNDS IN MYELOID LEUKEMIC CLONES CONTINUOUSLY CULTURED IN SERUM-FREE MEDIUM.

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Blood; 60(1):208-212 1982

Clones of myeloid leukemic cells varying in their competence for induction of differentiation have been continuously grown in serum-free medium. In the medium used, which contained transferrin, the growth rates of these cells were nearly similar to those found in serum-containing medium. The clones also maintained in this medium their competence for induction of differentiation by the normal macrophage and granulocyte differentiation-inducing protein MGI-2, the steroid dexamethasone, and lipopolysaccharide. In contrast to the results with these inducers, some clones continuously cultured in a serum-free medium showed a gain of inducibility by insulin and another clone a gain of inducibility by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate in low serum and serum-free medium. Induction of differentiation by these two compounds was therefore inhibited in these clones by the presence of serum. It is suggested that serum-free medium may also show the existence of other inducers of differentiation not detected in serum-containing medium and that these results are relevant to the possible therapeutic use of compounds such as insulin for the induction of normal differentiation in leukemic cells in vivo. (Author abstract) (24 Refs)

107. MECHANISMS OF TCGF PRODUCTION BY CLONED T-CELL LINES: CHARACTERIZATION OF PRODUCER LYMPHOMA LINES AND KINETICS OF PRODUCTION.

Smith RT, Shimizu S, Norcross MA, Maino VC
Tumor Biology Unit, Dept. Pathology, Univ. Florida, Coll. Medicine, Gainesville, FL, 32610
Clin Immunol Immunopathol; 23(2):286-296 1982

The activation requirements and kinetics of production of T-cell growth factor are described for a stable, cloned T-lymphoma line, EL4-G-12. The line yields a product which has the biochemical and biological attributes of TCGF of normal cell origin examined thus far. Production is dependent upon a transmembrane signal which can be provided by known T-cell-activating lectins, and by antibody to a specific ligand on the Thy-1 molecule, if accessory cells or factors are provided. Production is rapid, beginning within 4 hr, and ceasing between 12 and 18 hr depending upon cell density, signal intensity, and culture conditions. DNA synthesis ceases as production begins, and release is not a result of cell death. It has not yet been determined whether rapid synthesis de novo, or activation and release of an inactive hormone precursor explains the production kinetics observed. (Author abstract) (17 Refs)

108. STUDIES ON THE MECHANISM OF NATURAL KILLER (NK) CELL-MEDIATED CYTOTOXICITY (CMC). I. RELEASE OF CYTOTOXIC FACTORS SPECIFIC FOR NK-SENSITIVE TARGET CELLS (NKCF) DURING CO-CULTURE OF NK EFFECTOR CELLS WITH NK TARGET CELLS.

Wright SC, Bonavida B
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J Immunol; 129(1):433-439 1982

It was recently demonstrated that PHA-stimulated murine spleen cells will release soluble natural killer cytotoxic factors (NKCF) selective for NK target cells. The cytotoxic activity of NKCF directed against YAC-1 target cells can be detected by trypan blue uptake after an incubation period of 24 to 48 hr. The role of NKCF in NK cell-mediated cytotoxicity (CMC) reactions was investigated by determining whether the functional characteristics of NKCF conform with the known characteristics of NK activity as defined in the 51Cr-release assay. The following lines of evidence demonstrate that NKCF meet several criteria required to establish their possible role in the lytic mechanism of NK CMC. (1) NKCF are released by murine spleen cells during co-culture with NK-sensitive target cells over an incubation period of up to 48 hr. (2) The effector cell that releases NKCF is Thy-1.2 negative and asialo-GM1 positive. (3) Spleen cells from nude mice released high levels of NKCF, whereas mutant beige (bg/bg) mouse spleen cells release low levels. (4) NKCF lyse only NKA and NKB target cells (YAC-1, RL male 1, FLD-3, and WEHI-164) and non NK-resistant target cells (P815, EL4, AKSL2, R1.1, Molt-4, K562, and Raji). (5) The NK-sensitive YAC-1 cells absorb NKCF more effectively than the NK-resistant EL4 or AKSL2 cell lines. Taking available data of the NK CMC system and the characteristics of NKCF into consideration, a model is proposed for NK CMC reactions in which NKCF play an integral role in the lytic step. In this model, the effector cell must be able to recognize the NK-sensitive target and then release NKCF. On the other hand, for lysis to be achieved, the NK target cell must be able to activate the NK effector cell, to adsorb NKCF, and to be lysed by NKCF. (Author abstract) (17 Refs)

109. TRANSLATION OF MRNA FOR HUMAN GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR.

Lusis AJ, Golde DW, Quon DH, Lasky LA
Div. Hematology/Oncology, Dept. Medicine, UCLA Sch. Medicine, Los Angeles, CA, 90024
Nature; 298(5869):75-77 1982

Translation and partial characterization of a messenger RNA (mRNA) for human granulocyte-macrophage colony stimulating factors (GM-CSF) that stimulates both granulocyte and macrophage colonies are reported. The mRNA was isolated from human T-lymphocyte cell line, and when injected into Xenopus laevis oocytes it directed the synthesis of biologically active GM-CSF. The GM-CSF translated into oocytes also stimulated the growth in agar of a human myeloid leukemia cell line KG-1. As in the case of bone marrow cells, medium from oocytes injected with water or control RNA had no effect on the growth of KG-1 cells. However, homogenates of both injected and uninjected oocytes significantly inhibited cell growth. (21 Refs)

110. INHIBITION OF CYTOKINE PRODUCTION BY A TUMOUR CELL PRODUCT.

Farram E, Nelson M, Nelson DS, Moon DK
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Immunology; 46(3):603-612 1982

Supernatants from cultured mouse and human tumor cells, but not mouse or guinea-pig fibroblasts, inhibited the production of a lymphokine, macrophage chemotactic factor, by PHA-stimulated mouse spleen cells. The supernatants affected spleen cells from old, but not young, mice. They were most active if added at the start of the spleen cell culture and did not act by binding phytohemagglutinin (PHA). The active material had an approx mol wt, on membrane filtration, of 1,000-10,000 and could be bound to and eluted from Con A-Sepharose. Tumor supernatant factor(s) of similar mol wt inhibited the production of interleukin 1 (lymphocyte activating factor) in response to lipopolysaccharide by stimulated thioglycollate-induced peritoneal exudate macrophages, but not by Corynebacterium parvum-activated macrophages. Similar tumor-produced material has been found to inhibit the early phase of delayed-type hypersensitivity reactions in older mice. It is suggested that this effect is due, at least in part, to inhibition of interleukin 1 production leading to inhibition of lymphokine production. (Author abstract) (26 Refs)

111. HUMAN MONOCYTE MEDIATED CYTOTOXICITY TO K-562 CELLS: A FREEZE-FRACTURE-, SCANNING- AND THIN SECTION ELECTRON MICROSCOPIC STUDY.

Espevik T, Hammerstrom J, Halgunset J
Inst. Cancer Res. Trondheim, Univ. Trondheim, 7000 Trondheim, Norway
Acta Pathol Microbiol Immunol Scand [C]; 90(3):137-145 1982

The structural features of 'natural' human monocyte-mediated cytotoxicity towards K-562 leukemia cells in vitro have been examined. Human monocytes bound K-562 cells firmly and mediated a slow cytolysis of the leukemia cells. Monocyte binding of target cells was shown to be trypsin sensitive. Freeze-fracture and thin section electron microscopy revealed that effector and target cells were separated by an irregular space larger than 20 nm. There was no evidence for the involvement of specialized membrane junctions or organelle transfer between monocytes and target cells. Scanning electron microscopy revealed that K-562 cells bound to monocytes progressively lost their microvilli. This process started in the membrane areas close to the effector-target cell interaction. The results suggest that binding of target cells by monocytes followed by action of short-range soluble cytotoxic mediators may be the mechanism for the monocyte-mediated cytotoxicity towards K-562 cells. (Author abstract) (36 Refs)

112. THE EFFECT OF ALKYL-LYSOPHOSPHOLIPIDS (ALP) ON IN VITRO CLONOGENICITY OF NORMAL AND LEUKEMIC CELLS (MEETING ABSTRACT).

Vogler WR, Tidwell T, LaVia DS
Emory University, Atlanta, GA, 30322
Proc Am Assoc Cancer Res; 23:440 1982

Racemic 1-octadecyl-2-methyl-sn glycero-3-phosphocholine (ET-18-OCH3) is a lysophospholipid analog which has antitumor activity in vitro and in vivo. Cells containing an O-alkyl-cleavage enzyme are capable of metabolizing ALP and are not damaged. Cells lacking the enzyme are killed by the compound. Supposedly leukemic cells lack the enzyme and are relatively more susceptible than normals to injury by ALP. Leukemic blast cells obtained from bone marrow or peripheral blood and normal marrow cells obtained from patients (pts) without marrow disease were incubated at 37 C for 24 hours in RPMI medium containing 10% fetal bovine serum and 0, 5 and 10 ug/ml of ALP. The ALP was diluted to non-toxic concentrations and the cells plated in soft agar over a feeder layer containing a stimulator obtained from culture medium conditioned by human placenta. Cells were incubated 7 days at 37 C and clusters (15-40 cells) and colonies (greater than 40 cells) scored. Cells were obtained from 15 leukemic pts (8 acute myelocytic leukemia (AML), 2 acute lymphocytic leukemia (ALL), 2 chromic myelocytic leukemia (CML), 2 blastic phase of CML and 1 leukemic phase of diffuse histiocytic lymphoma) and 3 pts with normal bone marrows. No growth was observed in 4 leukemic pts and another had a heavy growth without discrete colonies. The remaining grew clusters and colonies. ALP at 5 and 10 ug/ml inhibited cluster-colony formation variably ranging from 5 to 83% reduction (average 51%). Five of eight showed a dose response effect, 3 did not, and 2 were not tested at 10 ug/ml. Three normal marrows showed a reduction in the number of macrophage-granulocyte clusters/colonies to 60% at 5 ug/ml and 48% at 10 ug/ml. These studies indicate that ALP has a variable inhibitory effect on the clonogenicity of leukemic cells and a less variable effect on normal marrow cells. (no Refs)

113. INDUCTION OF A MYELOID LEUKEMIA DIFFERENTIATION FACTOR (GM-DF) IN HUMAN POST ENDOTOXIN SERA (MEETING ABSTRACT).

Moore MA, Gabrilove J, Hirshaut Y, Pinsky C, Oettgen H
Memorial Sloan-Kettering Institute, New York, NY, 10021
Proc Am Assoc Cancer Res; 23:445 1982

Murine post-endotoxin sera contain high levels of myeloid colony stimulating factor(s) (GM-CSFs) and factors capable of inducing terminal granulocyte and macrophage differentiation of both the murine leukemic cell line M1 and the myelomonocytic leukemic cell line WEHI-3 (D+). The latter are separable from the bulk of GM-CSF. In conjuction with a Phase I trial of highly purified endotoxin in patients with advanced malignancy, we monitored human post-endotoxin sera for CSF and GM-DF. Sera obtained prior to and post intravenous injection of endotoxin (0.5, 2, 4, 6, 8, 12 and 24 hrs) administered on a biweekly schedule, were assayed for colony inhibitory activity and differentiation induction in semi-solid agar cultures of murine WEHI-3 myelomonocytic and human promyelocytic HL-60 leukemic cells. Baseline sera (10% v/v) showed little capacity to either induce differentiation or to inhibit leukemic cloning. A mild degree of colony inhibitory activity was noted in all post endotoxin sera with a peak effect occurring at the 0.5 hrs. Induction of colony differentiation activity was observed in all patients, and occurred maximally at 2-6 hrs. Following repeated injections of escalating doses of Novo Pyrexal, persisting serum levels of GM-DF were detected both pre and 24 hrs after treatment. Human active myeloid CSF was not detected in baseline sera but was induced with peak levels obtained at 6-8 hrs. Myeloid CSF appears to be a distinct activity from GM-DF since sources rich in CSF, possess low levels of GM-DF and vice versa. (no Refs)

CMI METHODOLOGY

114. DIFFERENTIATION BETWEEN LEUKEMIC AND NORMAL HUMAN LYMPHOCYTE LINES WITH A SIMPLIFIED RAPID SCREENING TEST FOR CELLULAR PLASMINOGEN ACTIVATOR (PA) (MEETING ABSTRACT).

Elashkar S, Reynertson S, Minowada J, Freedman HJ
University of Missouri Medical and Pharmacy Schools, 2411 Holmes, Kansas City, MO, 64108
In Vitro; 18(3,part2):284 1982

A simplified in vitro screening test has been developed for measuring fibrinolytic activity (PA levels) in leukemic and normal blood cell lines. By varying systematically all fibrin plate test parameters using a known PA-secreting cell line (PK1 porcine kidney), optimal lysis was seen with 10(5) cells/dish incubated for 20 hr at 37C. Thus 10(5) cells were inoculated in a 10-mm diameter central well made in a fibrin layer. The layer was produced by mixing bovine fibrinogen (14 mg/ml) and bovine thrombin (10 U/ml) in a 35-mm level tissue culture dish and permitting clot formation. Cells were placed in the well and without human plasminogen (PGN, 60 U/ml) incubated at 37C for 20 h, and the resulting lysis area measured. Quantitation of PA per cell was done with a standard curve relating lysis to that by streptokinase. The test has been used to measure PA activity in leukemic and normal lymphocyte cell lines. Normal lymphocyte (RPMI-1788) and leukemic B-cell (BALM-2) and T-cell (MOLT-4) lines were compared. Fibrinolytic activity in leukemia cells was 2-3 fold greater than in normal cells, and was due to PA by virtue of PGN-dependence. (no Refs)

115. EFFECT OF NOCARDIA RUBRA CELL-WALL SKELETON ON COLONY-STIMULATING ACTIVITY AND MYELOID COLONY FORMATION.

Ito M, Suzuki H, Nakano N, Yamashita N, Sugimori M, Sugiyama E, Maruyama M, Asanuma Y, Yano S
First Dept. Internal Medicine, Sch. Medicine, Toyama Medical and Pharmaceutical Univ., Sugitani, Toyama 930-01, Japan
Gann; 73(3):403-407 1982

The in vivo effect of Nocardia rubra cell-wall skeleton (N-CWS) was studied on the generation of bone marrow granulocyte-macrophage progenitor cells [colony-forming units culture (CFU-c)] and on the levels of myeloid colony-stimulating activity (CSA) in the conditioned medium of the lung (LCM) and serum obtained from mice. In vitro bone marrow culture showed that intraperitoneal (ip) treatment of mice with N-CWS markedly enhanced CFU-c formation induced by stimuli in LCM or serum derived from lipopolysaccharide (LPS)-treated mice. The LCM and serum of mice injected with N-CWS ip were also prepared and assayed for CSA. CSA levels with N-CWS-LCM as well as LPS-LCM used as the standard CSA were markedly greater than those achieved with control LCM. N-CWS-serum also showed a low but significant level of CSA. The CSA level of N-CWS-LCM was maximal at 3 to 5 days after N-CWS injection. These results raise the possibility that enhanced CSA production might be a major mechanism fo N-CWS stimulation of granulocyte-macrophage production. (Author abstract) (22 Refs)

116. DETECTION OF POLYOMA-VIRUS-INDUCED TUMOR ANTIGEN(S) BY MACROPHAGE MIGRATION INHIBITION.

Szigeti R, Dalianis T, Klein G, Ito Y, Magnusson G
Dept. Tumor Biology, Karolinska Inst., S 104 01 Stockholm, Sweden
Int J Cancer; 30(1):69-74 1982

We have applied the macrophage migration inhibition assay to study cell-mediated immune responses to antigens of polyoma-virus-transformed cells. Macrophages from polyoma-virus-immunized mice, but not from control mice, showed significant migration inhibition when exposed to extracts of polyoma-virus-induced mouse and rat transformed cells. Extracts of non-polyoma-induced tumors had no such effect. (Author abstract) (31 Refs)

117. A CELL-MEDIATED MUTAGENESIS ASSAY FOR DIMETHYLNITROSAMINE IN C3H/10T1/2 CELLS (MEETING ABSTRACT).

Mikles-Robertson F, Heidelberger C
University of Southern California Cancer Center, Los Angeles, CA, 90033
Proc Am Assoc Cancer Res; 23:361 1982

The C3H/10T1/2 mouse embryo fibroblast cell line is widely used as a quantitative system to measure oncogenic transformation and mutagenesis. These cells metabolize a number of chemical carcinogens, such as polycyclic aromatic hydrocarbons, to derivatives that produce cytotoxicity, mutagenicity, and cell transformation. However, these cells are incapable of activating some other classes of carcinogens, such as dimethylnitrosamine (DMN). Hence, an activation system has been developed, with emphasis on DMN. We use primary rat liver hepatocytes, prepared by a modification of the procedure of Jones and Huberman, as the activating system for C3H/10T1/2 target cells. The target cells and the hepatocytes are cocultivated for 24 hr at a target cell to hepatocyte ratio of 1:5; after treatment the cells are reseeded, and 24 hr later the selective agent, ouabain (3 mM) is added. Under these conditions DMN causes a dose-related cytotoxicity and mutagenesis; the relative plating efficiencies of the C3H/10T1/2 cells at 1 mM, 100 uM, and 10 uM DMN were 49%, 48%, and 92% respectively. The mutation frequencies X 10(6) were 116, 70.5, and 36.9. The control value was 2.6. In comparative studies of this cell-mediated activation system with S-9 liver homogenate induced with Aroclor 1254 and with an irradiated epithelial cell line (ML 21) derived from regenerating C3H mouse liver, significant activation of DMN was only achieved with the primary hepatocytes. (1 Ref)

SUPPRESSOR CELL ACTIVITY

118. SUPPRESSOR T CELLS ACTIVATED BY AUTOLOGOUS B-CELL DERIVED LINES INHIBIT BLASTOGENIC RESPONSES BY PERIPHERAL LYMPHOCYTES TO MITOGENS OR AUTOLOGOUS LYMPHOBLASTOID CELL LINES.

Tsukuda K, Tsukuda Y, Klein G

Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden

Cell Immunol; 69(2):291-304 1982

EBV-transformed B-cell lines (LCL) suppressed peripheral lymphocyte responses to mitogens (PHA, PWM, and protein A). Cell separation experiments have shown that LCL cells activate autologous radiosensitive suppressor T cells that inhibit T-cell responses to mitogens (PHA and Con A) and to the autologous lymphoblastoid cell line itself. The significance of this autologous response and the way it may reflect on the effect of the suppressor T cells on the regulation of potential autoimmune responses is considered in relation to the in vivo phenomena observed in the course of acute mononucleosis. (Author abstract) (37 Refs)

OTHER RELATED STUDIES

119. PRODUCTION OF HEPATITIS B E ANTIBODY IN EPSTEIN-BARR VIRUS-INDUCED B LYMPHOCYTE CELL LINES.

Furuya Y, Inoue M, Yoshida Y, Yoshihara N, Takada M

Kanagawa Prefectural Public Health Lab., 52-2 Nakao-cho, Asahi-ku, Yokohama 241, Japan

J Med Virol; 9(4):293-297 1982

A specific antibody-producing lymphocyte cell line (LCL) was established from peripheral blood lymphocytes of a donor carrying hepatitis B e (HBe) antibody (anti-HBe). Cultures were depleted of T-cells by removal of erythrocyte-rosetting cells, and were subsequently infected in vitro with Epstein-Barr virus. Upon initial establishment of the LCL anti-HBe could not be detected by solid-phase radioimmunoassay (RIA), double immunodiffusion, or reverse passive hemagglutination inhibition (R-PHI). However, after centrifugal harvesting of cells rosetting with HBe antigen-coupled sheep red blood cells the 10-fold concentrated supernatant showed the presence of anti-HBe by all three methods after 1 wk. The anti-HBe titer was 64-fold at 1 wk, 256-fold at 2 wk, 128-fold at 3 wk, but undetectable at 5 wk using R-PHI. RIA could not detect anti-HBe after 5 wk either. Anti-HBe activity in the culture supernatant was not destroyed by treatment with 0.2 M 2-mercaptoethanol at 2 wk, indicating that the antibody was not sensitive to this agent. and that the anti-HBe was IgG. The decline in anti-HBe activity in long-term cultures was not associated with any change in growth pattern. (12 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Adelson LJ........ 34
Aderka D........ 94
Aikat BK........ 93
Akane H........ 19
Aleksa TV........ 31
Alford TC........ 49
Alley L........ 39
Alter BP........ 45
Amemiya K........ 53
Andrade-Mena CE........ 84
Andreotti PE........ 74
Aoki T........ 87
Arika T........ 53
Arika T........ 77
Armerding D........ 59
Asanuma Y........ 115
Azocar J........ 67
Babbage J........ 23
Baecher-Steppan........ 60
Baechtel FS........ 102
Baehner RL........ 105
Ballester JM........ 14
Barnabei V........ 3
Baroni CD........ 15
Barsky SH........ 49
Beardsley T........ 50
Bechtold T........ 3
Bell BS........ 47
Benoist H........ 86
Berardet M........ 84
Berel E........ 64
Bloomfield CD........ 18
Bonaventure J........ 46
Bonavida B........ 108
Borden EC........ 6
Bostick-Bruton........ 38
Boucheix C........ 16
Bouchet C........ 86
Bowlin TL........ 66
Boxer LA........ 105
Boxer LA........ 41
Boyd AW........ 96
Brailovsky C........ 46
Braun DP........ 33
Braun DP........ 4
Brooker AS........ 34
Brovall C........ 42
Bugelski PJ........ 101
Buimovici-Klein........ 2
Burns WH........ 43
Bygbjerg I........ 1
Cadiou M........ 16
Callard RE........ 23
Camacho ES........ 21
Camacho SA........ 21
Cameron DJ........ 92
Cannon GB........ 49
Carbone G........ 91
Carchman RA........ 100
Carlquist JF........ 39
Carson DA........ 13
Centurioni R........ 20
Chang YC........ 6
Chartrand SL........ 18
Chu-Louis J........ 17
Ching C........ 44
Ching N........ 44
Chirigos MA........ 70
Coccia P........ 42
Coffey RG........ 97
Cohen SA........ 83
Colombo MP........ 91
Cooper MD........ 104
Crawford G........ 90
Cruz C........ 14
Da Cunha Gomes........ 75
Dalianis T........ 116
Danieli G........ 20
Dao TL........ 6
Davey FR........ 37
Dawson JR........ 85
De Oliveira CA........ 75
De Paiva Rebelo........ 75
Dean JH........ 49
Denny TN........ 95
Desplaces A........ 86
Dickmeiss E........ 1
Dock NL........ 37
Dubey DP........ 67
Dufer J........ 86
Dvorak AM........ 7
Dvorak HF........ 7
Eberlein TJ........ 54
Edelstein R........ 27
Eggen BM........ 81
Ehrke MJ........ 83
Elashkar S........ 114
Elhilali M........ 46
Enk C........ 1
Erdmann T........ 24
Ernberg I........ 5
Escribano L........ 16
Espevik T........ 111
Essex M........ 67
Evans DL........ 61
Farmer JL........ 102
Farram E........ 110
Fauci AS........ 40
Fauci AS........ 41
Feldman M........ 72
Fernandes G........ 95
Fernandez NL........ 14
Fialho F........ 75
Fink U........ 12
Fisher RI........ 38
Fishman M........ 90
Fong S........ 13
Ford C........ 39
Foschi A........ 15
Fox RI........ 13
Freedman HJ........ 114
Frenkel EP........ 29
Frenster DA........ 30
Frenster JH........ 30
Friedman-Kien A........ 2
Fujisawa T........ 52
Fujiwara M........ 53
Furuya Y........ 119
Futrell JW........ 51
Gabrilove J........ 113
Gadol N........ 63
Gajl-Peczalska........ 18
Gerstoft J........ 1
Geyer SJ........ 51
Golde DW........ 109
Goldrosen MH........ 58
Good RA........ 95
Gordon WC........ 102
Gorelik E........ 72
Graham R........ 21
Grinevich IuA........ 10
Gupta N........ 93
Gupta SK........ 56
Gupta SK........ 62
Gutterman JU........ 6
Haahr S........ 1
Haas M........ 50
Hadden EM........ 97
Hadden JW........ 97
Halberg P........ 1
Halgunset J........ 111
Haliotis T........ 41
Hamilton TA........ 90
Hammerling U........ 73
Hammerstrom J........ 111
Hanjan SN........ 104
Harada S........ 3
Harris JE........ 33
Harris JE........ 4
Harris LS........ 100
Harris NL........ 7
Hasek M........ 88
Hauser WE........ 69
Hawrylko E........ 57
Hayashi M........ 98
Heidelberger C........ 117
Heidemann E........ 80
Hengst JC........ 34
Herberman RB........ 40
Hernandez P........ 14
Hersh EM........ 22
Hill S........ 29
Hill S........ 50
Hirshaut Y........ 113
Holland JF........ 45
Holland JF........ 6
Hollingsworth M........ 61
Honma Y........ 98
Howell S........ 48
Hozumi M........ 98
Hraba T........ 88
Huard TK........ 36
Hudemann B........ 24
Ibrahiem EH........ 46
Iguchi K........ 19
Inoue M........ 119
Israel L........ 27
Ito M........ 115

Ito Y 116
Ito Y 99
Izawa T 19
Jackson H 103
Jackson L 43
Jacobsen M 1
Jansa P 25
Jensen K 1
Jensen PJ 78
Jerome LF 49
Jim R 44
Jonasson J 50
Kabelitz D 12
Kalra DS 56
Kalra DS 62
Kan-Mitchell J 34
Kapoor AK 9
Kapp DS 76
Kappany H 46
Katz P 40
Kayibanda M 16
Kearney JF 104
Kempf RA 34
Kerdel FA 32
Kerkvliet NI 60
Kharole MU 56
Kharole MU 62
Kikuchi K 29
Kim KS 2
Kimura H 52
Kimura S 73
Kirmani N 43
Klein E 5
Klein G 116
Klein G 118
Klein G 5
Knight WA 47
Koessler A 48
Kohl S 65
Komatsu N 77
Konishi K 35
Koren HS 78
Koyama S 71
Kozbor D 41
Krim M 70
Krug K 26
Kruger W 26
Kumar A 9
Kurec AS 37
Kushwala MR 9
LaPushin R 22
LaVia DS 112
Lafuma J 64
Laing L 41
Landy M 89
Lane RL 100
Laskin DL 100
Lasky LA 109
Lassus M 45
Lau W 44
Laubenstein LJ 2
Lavie G 94
Lawrence W 100
Leoni P 20
Levine G 51
Lewis DA 58
Lipsky P 29
LoBuglio AF 36
Loh K 44
Loo LS 65
Look AT 90
Lorenzen I 1
Lusis AJ 109
MacDonald DM 32
Magnusson G 116
Maino VC 107
Malchow-Moller 1
Manischewitz JF 43
Mantich NM 105
Marchegiani G 20
Marcorelli E 15
Marie JP 16
Marmor M 2
Marshall D 28
Martyre MC 16
Maruyama M 115
Masek MA 30
Masse R 64
Mastrangelo MJ 70
Masucci MG 5
Mathe G 84
Matheson DS 41
Matsuda T 19
Matsuo T 77
Mauldin S 102
Mavligit GM 22
Mavrichev AS 31
McCaughan GW 23
McCluskey DR 8
McCoy JL 49
Mehrotra RM 9
Mejer J 1
Micksche M 11
Miguez LA 75
Mihich E 83
Mikawa H 99
Mikles-Robertso 117
Miller C 44
Minowada J 114
Mitani M 77
Mitchell M 70
Mitchell MS 34
Miyanomae T 99
Mokhort VA 31
Montillo M 20
Montroni M 20
Moon DK 110
Moore M 79
Moore MA 113
Morais de Sa CA 75
Morales A 68
Moreschi G 43
Morgan EW 32
Mori KJ 99
Moriyama M 55
Mostowski H 41
Muller G 26
Nakano N 115
Nakoinz I 103
Nelson DS 110
Nelson M 110
Neuwelt EA 29
Newcomb TF 47
Nielsen JO 1
Niethammer D 80
Nigam V 46
Nishioka K 19
Nolibe D 64
Norcross MA 107
Occhionero M 15
Oettgen H 113
Ohnuma T 45
Okabe-Kado J 98
Orbach-Arbouys 84
Pace R 28
Paciucci PA 45
Paik Y 44
Pang AS 68
Parmiani G 91
Patel J 6
Patt YZ 22
Pattengale PK 50
Perrot JY 16
Pick AI 94
Pick E 89
Pierce G 42
Pierotti MA 91
Pinkhas J 94
Pinsky C 113
Pollack MS 17
Polmar S 42
Poste G 101
Prager MD 102
Proffitt MR 66
Pross H 41
Purtilo DT 3
Quinnan GV 43
Quon DH 109
Rabson JA 51
Ralph P 103
Rassoul F 26
Rastetter J 12
Rathi AK 9
Reichert A 12
Reichmann U 80
Remington JS 69
Reynertson S 114
Richman S 82
Richter V 26
Riedel H 24
Riegrova D 25
Rockwell S 76
Roder JC 40
Roder JC 41
Rodrigues MA 75
Rogers G 3
Ron Y 72
Roodman GD 47
Rook AH 43
Rosenberg SA 54
Rosenfeld C 16
Rosenstein M 54
Rothbart RK 34
Rubin P 41
Rubinstein P 2
Ruco L 15
Sachs L 106
Sadlik JR 97
Safai B 17
Sakamoto K 3
Sakita T 71
Sakurai M 19
Saluk PH 63

Samak R 27
Santos GW 43
Santos MN 14
Saracino RT 86
Saral R 43
Schacter B 42
Schechter P 21
Schrader JW 96
Seeley J 3
Segal S 72
Sehgal S 93
Seto D 44
Seyfarth M 24
Shaklai M 94
Sharma SD 69
Shau H 85
Shimizu S 107
Shoenfeld Y 94
Simons SM 34
Slovin SF 13
Smith BM 100
Smith J 7
Smith RT 107
Solvay MJ 36
Sondergaard J 1
Souhami RL 23
Spiess P 54
Spigland I 2
Stahl R 2
Staunton D 67
Steinberg J 102
Sturm RJ 100
Stux S 67
Sugimori M 115
Sugiyama E 115
Suzuki H 115
Suzuki M 53
Svedmyr E 5
Swartz WM 51
Symonds G 106
Szigeti R 116
Szigeti R 5
Tada N 73
Taetle R 48
Takada M 119
Talpaz M 22
Tanimoto Y 19
Tatum K 82
Taylor CR 50
Taylor GM 79
Thomsen HK 1
Tidwell T 112
Tinley V 49
Tomonari K 73
Treuner J 80
Tsoukas CD 13
Tsubura E 87
Tsukuda K 118
Tsukuda Y 118
Tsurusawa M 99
Tuteja N 9
Twomey P 50
Uccini S 15
Uchida A 11
Urushizaki I 87
Vahey AL 33
Vanderzee J 102
Vaughan JH 13
Vogler WR 112
Wanebo HJ 28
Wasserman LR 45
Watson JD 103
Weksler ME 73
Wells RJ 105
Werner H 24
Wesley R 54
White JG 41
White WJ 79
Wiener L 6
Wilkinson R 44
Williams N 103
Wilms K 80
Wong L 44
Wright SC 108
Wright TL 47
Wustrow TP 95
XLP Collaborato 3
Yamaguchi Y 52
Yamashita N 115
Yano S 115
Yasaka T 105
Yetz J 3
Yoshida Y 119
Yoshihara N 119
Yoshioka T 71
Yoshitsugi H 44
Yunis EJ 67
Zamkoff KW 37
Zaytoun AM 40
Zittoun R 16
Zolla-Pazner S 2

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DECEMBER, 1982

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In this issue:

- **EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS** 1-45
- **EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS** 46-77
- **EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION** 78-110
- **THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE** 111-128
- **RELATED BIOLOGY OF IMMUNE CELLS** 129-133
- **CMI METHODOLOGY** 134-137
- **SUPPRESSOR CELL ACTIVITY** 138-142
- **OTHER RELATED STUDIES** 143-146

EVALUATION OF CELL MEDIATED IMMUNITY IN HUMAN SUBJECTS

1. CIRCULATING SUPPRESSOR MONOCYTES IN MALIGNANT DISEASE.

Berlinger NT
University of Minnesota, Minneapolis, MN
Diss Abstr Int [B]; 42(10):4008-B 1982

T-lymphocyte proliferation in mixed leukocyte culture was measured for normal individuals and for patients with squamous cell carcinoma of the head and neck. Normal responsivness calculated by the relative response method was established to be 68% or greater. Cancer patients frequently showed abnormally low levels of T-cell proliferation. When patient macrophages were removed from the mixed cell cultures, significantly increased levels of T-cell proliferation often occurred in previously poorly reactive cultures. Macrophages were removed by filtering patient peripheral blood leukocytes through columns of Sephadex G-10 beads. Fractions of irradiated immune cells were added back to mixed cell cultures of patient macrophage-depleted lymphocytes which showed significantly increased T-lymphocyte proliferation after macrophage remov-

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al. The fractions which were depleted of macrophages by G-10 column filtration or which were enriched to T-cells by rosetting with sheep erythrocytes showed no significant suppression of T-lymphocyte proliferation. The fraction which did not rosette with sheep erythrocytes showed significant suppression of T-lymphocyte proliferation as did unseparated peripheral blood leukocytes. In short only those fractions which contained macrophages or were enriched for macrophages showed any evidence of suppression of autologous patient T-cells. Cancer-free individuals from family aggregates of seemingly hereditary colon cancer were similary studied and some also showed evidence of suppressor macrophages. This indicated that the appearance of the suppressive cell in some instances could perhaps antedate the appearance of a tumor. Macrophages of normal individuals also was able to suppress autologous T-lymphocyte proliferation in mixed leukocyte culture. However, macrophages from cancer patients were significantly more efficient suppressor cells, indicating that excessive macrophage suppression with cancer may be a perturbation of a normal homeostatic mechanism. (no Refs)

2. STUDY ON T-CELLS BEARING FC RECEPTORS FOR IGG IN PATIENTS WITH CANCER OF DIGESTIVE ORGANS.

Taki M
Dept. Surgery, Okayama Univ. Medical Sch., Okayama, Japan
Nippon Gan Chiryo Gakkai Shi; 17(3):720-727 1982

T- and Tgamma-cell populations were measured in 23 healthy controls, 9 controls with benign diseases, and 68 patients with gastrointestinal cancers (46 gastric, 16 rectal, 3 esophageal, and 3 pancreatic), and the relationships of the Tgamma-cell populations to other immunological parameters were studied. Also, the antibody-dependent cellular cytotoxicity (ADCC) and natural killer (NK) activities of various fractions of peripheral lymphocytes were determined. Tgamma-cells were detected with the aid of double-rosette forming method using non-coated sheep RBC and rabbit IgG antibody-coated chicken RBC. Tgamma-cell percentages were higher in the patients with cancer than in the controls. Compared to that of controls (5.4 +-2.1%), percentages of Tgamma-cells were 4.7 +-2.2% in patients with Stage I gastric cancer, 5.9 +-2.7% in Stage II, 8.5 +-3.9% in Stage III, and 8.7 +-4.4% in Stage IV. Percentages of Tgamma-cells increased with respect to increased Stage of the cancers, and the percentages returned to within the normal range when tumors were extirpated. ADCC and NK activities of the fractions of lymphocytes were highest in the Tgamma-rich fractions, and decreased in the order of T-rich, B-rich, and T non-gamma-rich fractions. No differences in the activities of each fraction were observed between the lymphocytes from the controls and cancer patients. (16 Refs) (In JPN)

3. PERIPHERAL T-LYMPHOCYTES AND DELAYED HYPERSENSITIVITY IN SURGICALLY AND RADIOLOGICALLY TREATED PATIENTS WITH EARLY STAGES OF LARYNX-CARCINOMA.

Behrens K, Sesterhenn K, Schutt A
Universitats-HNO-Klinik, Joseph-Stelzmann-Strasse 9, D-5000 Koln 41, W. Germany
HNO; 30(7):250-255 1982

One hundred twenty-two patients with squamous-cell-carcinoma of the larynx (T1-stage) were examined after surgical or radiological treatment. None of these patients showed evidence of tumor recurrence. Peripheral T-lymphocytes and delayed hypersensitivity were studied in all these patients. According to their treatment, the patients were allotted into three groups and compared with a control group, consisting of 20 patients with nonneoplastic head- and neck-disease. The main finding was a significant decrease in the peripheral T-lymphocytes in surgically- or radiologically-treated patients with a squamous-cell-carcinoma of the larynx (T1-stage). This reduction of T-cells must be interpreted as a congenital or acquired defect of the immunocompetent system. In about half of the control cases the DNCB-tests showed no evidence of delayed hypersensitivity. In view of these results and those reported in the literature, the test should be used critically. In contrast to our earlier findings, where patients received radiotherapy over large areas including big vessels, radiation over a smaller, localized area does not lead to a significant depression of peripheral T-lymphocytes. (Author abstract) (21 Refs) (In GER)

4. QUANTITATION OF PROLIFERATIVE AND CYTOTOXIC PRECURSOR CELLS DIRECTED AGAINST HUMAN TUMOURS: LIMITING DILUTION ANALYSIS IN PERIPHERAL BLOOD AND AT THE TUMOUR SITE.

Vose BM
Dept. Immunology, Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England
Int J Cancer; 30(2):135-142 1982

Blood and tumor-infiltrating lymphocytes (TIL) from 16 cancer patients have been examined under limiting dilution conditions to determine the frequency of cells responding in mixed tumor-lymphocyte cultures (MLTC) to autologous tumor and interleukin-2 (IL-2). Tumor-derived lymphocytes showed a high spontaneous response to IL-2 alone 1/1,900 in TIL; 1/6,000 in PBL suggesting the presence of 'activated' T cells in situ. Proliferative frequencies were increased in MLTC in both blood (1/3,779) and TIL (1/1,084). Phenotypic analyses showed that total T-cell contents of the responder populations were comparable but TIL were enriched for the OKT8+ subset with a corresponding reduction in OKT4+. TIL showed increased numbers of OKMI+ and Tac+ lymphocytes. The major cytotoxic precursor expanding under these conditions was reactive against autologous tumor. K562 (NK) were present at a lesser frequency - particularly in TIL. The data show a concentration and activation of reactive lymphocytes at the tumor site and establish conditions for the clonal expansion of specifically cytotoxic T cells. (Author abstract) (35 Refs)

5. RELEASE OF LYMPHOTOXIN BY CONTROL AND CHEMICAL CARCINOGEN-TREATED LYMPHOCYTE CULTURES DERIVED FROM BLACK HEALTHY SUBJECTS AND CANCER PATIENTS.

Alfred LJ, Venkatesan N, Mandal AK, Gill G, Richardson M, Williams C, Bradley C
Pathology Dept., Charles R. Drew Medical Sch., 1621 East 120th St., Los Angeles, CA, 90059
J Natl Med Assoc; 74(8):775-781 1982

In an age-adjusted comparison with white men, black men have a significantly higher increase in esophageal and other types of cancer associated with environmental causes. The basis of this increase in cancer rates in blacks over the last two decades is unknown. Since cancer patients generally show an impairment in cell-mediated immune (CMI) functions, we measured certain CMI reactions in cultured lymphocytes derived from black healthy subjects and cancer patients. We also determined the levels of aryl hydrocarbon hydroxylase (AHH) induced in these lymphocytes. AHH catalyzes the activation of polycyclic aromatic hydrocarbons (PAH) to intermediates which might alter CMI functions. Lymphocytes from 33 black patients with squamous cell carcinoma and 22 healthy volunteers were mitogen-activated with phytohemagglutinin and concurrently treated with the environmental carcinogen, 3-methylcholanthrene (MCA). Measurements were made of the effects of MCA (0.5 to 3.0 uM) on blastogenesis, T-cell growth, lymphotoxin (LT) release, and AHH induction in these lymphocyte cultures. MCA treatment depressed blastogenesis but had no depressive effect on T-cell growth in cultures. Blastogenesis and T-cell growth were mitogen dose-dependent, while LT release was independent of mitogen concentrations. There was a significantly lower LT release by lymphocytes from lung cancer patients, compared to those from healthy and head/neck cancer subjects. The reduced levels of LT release in lung cancer patients might reflect an impairment in this CMI function. Studies on the role of lymphocyte subpopulations in CMI functions are in progress. (Author abstract) (27 Refs)

6. T LYMPHOCYTE SUBSETS FOLLOWING RADIATION THERAPY AND AFTER X-RAY EXPOSURE OF T CELLS IN VITRO (MEETING ABSTRACT).

Petrini B, Wasserman J, Blomgren H
Karolinska Hospital, Stockholm, Sweden
Scand J Immunol; 15(1):133 1982

T lymphocyte subpopulations were examined before and after post-operative radiation therapy in breast cancer patients. Tg cells (with Fc receptors for IgG) decreased in contrast to Tm cells (with Fc receptors for IgM). Proportions of suppressor- and helper- T cells determined by FITC-conjugated monoclonal antibodies (LEU 2A and LEU 3A, respectively) were not affected. X-ray exposure of T cell suspensions reduced Tg cells in contrast to Tm cells, while proportions of LEU 2 and LEU 3 cells were not changed. Thus in vitro experiments corroborated results obtained in vivo. (no Refs)

7. PROGNOSTIC SIGNIFICANCE OF THE OCCURENCE OF SUPPRESSOR CELLS IN PATIENTS WITH ADVANCED GASTRIC CANCER (MEETING ABSTRACT).

Uracz W, Mytar B, Ruggiero I, Popiela T, Zembala M
Division of Clinical Immunology, Institute of Paediatrics, Copernicus Medical School, Cracow, Poland
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Most workers found that depressed cell-mediated immunity including lymphocyte response in vitro correlates with the stage of disease and a poor prognosis. One of the possible mechanisms responsible for the impaired lymphocyte response in vitro may be predominantly monocytes. In the present studies the occurrence of suppressor cells (SC) was investigated in a group of patients with localized and advanced gastric cancer before any therapy. It was found that depressed lymphocyte response to mitogen in advanced cancer was related to the appearance of SC. The increased occurrence of SC was related to the tumor burden. Patients with advanced gastric cancer and demonstrable SC at the time of diagnosis and a significantly increased survival in comparison to those without SC. Although there was an inverse correlation between the presence of SC and the magnitude of lymphocyte PHA response, the latter had no prognostic value. These observations indicate that in patients with advanced gastric cancer and generally poor clinical prognosis, the presence of SC may be an indicator of favorable clinical outcome and suggests that the common view that depressed lymphocyte response in vitro correlates with poor prognosis, may not be valid in all types of cancer. (2 Refs)

8. THE STUDY OF PERIPHERAL T-CELL SUBPOPULATIONS IN PATIENTS WITH HODGKIN'S DISEASE PERFORMED BY MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Del Giacco GS, Cengiacott L, Locci F, Mathieu A, Mantovani G, Di Tucci A, Broccia G, Indiveri F
Clinical Immunology, University of Cagliari Medical School, Cagliari, Italy
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Peripheral T-cell subpopulations of 15 patients with Hodgkin's (HD) disease and off-therapy for at least 5 years, and of 7 patients with the disease at its beginning have been studied by means of various techniques: E-rosette formation, response to polyclonal mitogens, immunofluorescence and by monoclonal antibodies specific for lymphocyte antigens OKT3 (total T-cells), OKT4 (T-helper mainly), OKT8 (T-suppressor/cytotoxic mainly) of the Ortho series and by monoclonal antibodies anti-Ia like antigens. The percentage and the absolute count of OKT8 positive cells have been found increased compared to normal subjects (26.7%+/-5 vs 20+/-4) both in long survivors and in new patients independently from their stage and/or histological type. OKT4 positive cells are in the normal range (about 45%) when the absolute count is considered. Also OKT3 positive cells are in the normal range (64% vs 67.5%) whereas E-rosette forming cells are, as already known, reduced as the percentage and the absolute count are concerned, suggesting the influence of factors present in serum inhibiting the ability of rosette forming cells. No Ia-like antigens bearing cells have been identified among purified T-cells of peripheral blood in HD. Our data confirm an imbalance of T-cell subpopulations in HD. (no Refs)

9. SELECTIVE IMMUNOSUPPRESSION BY TOTAL LYMPHOID IRRADIATION: APPLICATIONS IN AUTOIMMUNE DISEASE AND ORGAN TRANSPLANTATION (MEETING ABSTRACT).

Kaplan HS
Division of Radiation Therapy, Stanford University Medical Center, Stanford, CA, 94305
Twenty-fourth Annual Meeting of the American Society of Therapeutic Radiologists, October 25-29, 1982, Orlando, Florida American Society of Therapeutic Radiologists; 1982

The technique of total lymphoid irradiation (TLI) was developed at Stanford in 1962 for the treatment of patients with Stage III Hodgkin's disease and other malignant lymphomas. Long term observations are now available on hundreds of patients treated by this technique to essentially all of the lymphoid tissues of the human body. The only clinically overt immunologic effects of TLI have been an increase in susceptibility to herpes zoster-varicella virus infection and one well-documented case of radiation-induced splenic atrophy, complicated by fatal pneumococcal sepsis. In vitro studies revealed that TLI induces a profound T-lymphocytopenia which may persist for 10 years or more after successful radiotherapy for Hodgkin's disease. The T-lymphocytopenia is accompanied by profound abnormalities of T-lymphocyte reaction which may persist for 2-5 years and an impairment of responses to PHA and other lectins which may persist for 10 or more years. These observations suggested that TLI might be useful as an immunosuppressive regimen for patients undergoing organ and tissue transplantation, as well as in patients with severe autoimmune disease. Laboratory investigations in mice, rats, dogs, and monkeys have confirmed the remarkable efficacy of TLI as a conditioning regimen in organ and tissue recipients. The cellular mechanisms underlying these immunosuppressive effects of TLI have been extensively investigated and point strongly to the induction of populations of suppressor cells which block both host-vs-graft and graft-vs-host reactions. Preliminary clinical investigations are now in progress to assess the efficacy of TLI in the treatment of patients with refractory rheumatoid arthritis and with systemic lupus erythematosus and impaired renal function, as well as in patients undergoing organ transplantation. (no Refs)

10. PROSTAGLANDIN RELATED AND ADHERENT CELL SUPPRESSOR SYSTEM IN APPARENTLY CURED HODGKIN'S DISEASE (HD) PATIENTS (MEETING ABSTRACT).

Haim N, Meidav A, Samuelly B, Segal R, Robinson E
Department of Oncology, Rambam Medical Center, Haifa, 35 245, Israel
Proc Am Soc Clin Oncol; 1:C-174 1982

Two suppressor systems of mononuclear cells were investigated in 22 patients (pts) with HD and in 25 healthy controls. The pts were previously treated by radiotherapy, MOPP (nitrogen mustard, vincristine, prednisone, procarbazine) combination or by a combination of radiotherapy and chemotherapy. All pts had no evidence of disease at the time of the study and the disease-free interval ranged between 1.5 to 14 years. The prostaglandin related suppressor system (PgSS) was tested by adding indomethacin 1mg/ml to lymphocyte cultures. The adherent cell suppressor system (ACSS) was tested by removal of the adherent cells on plastic petri dishes. The PgSS index of suppression was defined as the ratio of lymphocyte proliferation (LP) by phytohemagglutinin (PHA) with indomethacin to LP without indomethacin. The ACSS index was defined as the ratio of LP by nonadherent cells to the total LP. The mean PgSS index in pts was significantly higher than in controls. The ACSS index in pts was also higher than in the controls. LP by PHA in pts was significantly lower than in controls. Seven of 22 pts had PgSS index of 1.3 or higher and no one of the controls reached such a value. Pts who had a PgSS index of 1.3 or higher had a significantly lower LP than pts who had a PgSS index lower than 1.3. This study indicates that persistent immune abnormalities in apparently cured HD pts could be related to an increased suppressor activity of mononuclear cells. (no Refs)

11. IMMUNOLOGICAL INVESTIGATIONS IN LARYNGEAL CANCER.

Krajina Z, Bolanca S
Dept. Otolaryngology, Univ. Zagreb, Zagreb, Yugoslavia
Excerpta Med Int Congr Ser; 582:89-93 1982

Clinical investigations of the immunological status of 41 patients with laryngeal cancer are reported. Seventeen of 41 patients responding to dinitrochlorobenzene (DNCB) survived 1-3 yr. A positive reaction to DNCB was associated with a better prognosis, but a negative response should not be considered a contraindication to surgery. The test for purified protein derivative had less prognostic significance. The phytohemagglutinin (PHA) test values decreased from a mean of 44% in patients with localized disease to 25-26% in those with metastases and recurrences; a mean of 54% was found in cured patients. In patients with a strong lymphocyte reaction of the tumor, no recurrence or metastases occurred, regardless of the tumor's size. The lymphocyte reaction of surrounding structures should also be determined as an indirect indication of the organism's specific reaction to tumor antigens. All patients tested with laryngeal and hypopharyngeal cancer had values of PHA and T-lymphocytes at least 50% below normal levels, while these values were normal in patients with skin cancer. In vitro reaction to tumor antigens is not helpful in predicting the outcome of laryngeal cancer. Immune reaction tests should be performed on all patients with laryngeal cancer. If all tests are normal (a rare finding), prognosis is good. (10 Refs)

12. THE IMPORTANCE OF T-LYMPHOCYTES IN CHEMOTHERAPY OF LYMPHOID MALIGNANCIES IN CHILDREN.

Kadagidze ZG, Makhonova LA, Tabagari DZ, Zhogoleva IB, Mayakova SA, Susuleva NA

Center for Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR

Vopr Onkol; 28(5):104-109 1982

The levels of T-lymphocytes in untreated lymphoid malignancies in children and those after different schemes of chemoimmunotherapy were compared. The ratio of T-helper and T-suppressor cells changed in the course of treatment in correlation with the chemotherapeutic effect: the fraction of Tmu cells practically did not change whereas the Tgamma cell fraction decreased considerably in patients who revealed a good response to therapy. BCG treatment stimulated both populations but the response of Tgamma cells was stronger. Transplantation of thymus was followed by an increase in Tmu cells. (Author abstract) (22 Refs) (In RUS)

13. IMBALANCE OF T CELL SUBPOPULATIONS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA OF THE B CELL TYPE.

Herrmann F, Lochner A, Philippen H, Jauer B, Ruhl H

Dept. Hematology and Oncology, Klinikum Steglitz, Free Univ. Berlin, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany

Clin Exp Immunol; 49(1):157-162 1982

T cell enriched mononuclear cells from the peripheral blood of 20 patients with histologically and immunologically defined chronic lymphocytic leukemia of the B cell type (B-CLL) and 20 healthy individuals of various ages were investigated with T cell-specific monoclonal antibodies (OKT 4 and OKT 8) with regard to their subpopulation distribution. In B-CLL, a significant increase of lymphocytes reacting with OKT 8 could be demonstrated. Whereas there was a ratio of OKT 4 to OKT 8 of 1.72 in the control group, and OKT 4 to OKT 8 ratio of 0.67 was found in the B-CLL as a whole. With increasing clinical stage in accordance with the Rai scheme, a further displacement of this ratio in favor of OKT 8 positive cells was found. These results clearly show that, in peripheral blood of patients with B-CLL, an abnormal distribution pattern of circulating T cell subpopulations is present and that this also has prognostic relevance. (Author abstract) (24 Refs)

14. REDUCED T-COLONY FORMING CAPACITY IN B-CHRONIC LYMPHOCYTIC LEUKAEMIA. II. CORRELATION WITH CLINICAL STAGE AND FINDINGS IN B-PROLYMPHOCYTIC LEUKAEMIA.

Foa R, Lauria F, Catovsky D, Galton DA

I Cattedra di Patologia Speciale Medica, Istituto di Medicina Interna, Corso Polonia 14, 10126 Torino, Italy

Leuk Res; 6(3):329-333 1982

T-colony growing capacity of samples obtained from 33 patients with B-cell chronic lymphocytic leukemia (B-CLL) and 5 with B-cell chronic prolymphocytic leukemia (B-PLL) was studied to investigate the correlation with Rai's clinical staging and the proportion of circulating T-lymphocytes with suppressor phenotype (T-gamma). All patients were untreated or had been off therapy for at least 5 mo. According to Rai's staging, 9 B-CLL patients had Stage 0 disease, 8 Stage I, 14 Stage II, and 2 Stages III-IV. The overall proportion of T-gamma cells was significantly increased in both B-CLL and B-PLL compared with normal controls. The proportion of T-lymphocytes with helper phenotype (T-u) was significantly reduced in both diseases. In B-CLL the mean number of T-colonies (mean 31 +-32.5) was significantly lower than with normal T-lymphocytes (mean 121 +-36.1). T-colony forming capacity was related to the clinical stage of the disease. Seven of the 9 Stage 0 samples gave rise to more than 50 colonies (77.7%), while only 5/24 Stages I-IV samples (20.9%) gave the same number of colonies. In four of the five B-PLL tested, the T-colony growth of the purified T-lymphocytes was markedly reduced. The T-colony numbers and the percentage of T-gamma cells were correlated in 26 patients with B-CLL and B-PLL. Results indicated that the T-colony forming capacity appears correlated to disease progression. (13 Refs)

15. ABNORMAL T LYMPHOCYTE SUBPOPULATIONS DETECTED WITH MONOCLONAL ANTIBODIES IN CHRONIC LYMPHOCYTIC LEUKAEMIA (MEETING ABSTRACT).

Choremi H, Kofina A, Constandinidou N, Economidou J, Nikiforakis E, Papajannis A, Constantoulakis M

Department of Immunology and Department of Haematology-Lymphoma, Evangelismos Hospital, Athens, Greece

Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

The proportion of T lymphocyte subsets (ER, OKT3, OKT4, OKT8) was studied in 14 untreated patients with B-cell chronic lymphocytic leukemia (CLL) and 10 normal subjects. The results were expressed as percentage of total lymphocytes. The patients were grouped according to the Rai staging. The corresponding results in the controls were for ER=84.3 +/-5.2, for OKT3=72.4 +/-8.4, for OKT4=52 +/-7.8 and for OKT8=25.8 +/-4.6. The percentage of the T cell subpopulations was very low in all patients. The ratio T4/T8 was significantly lower in the patients than in controls, but there was no significant difference between the two groups. In 5 cases E-rosette positive lymphocytes were isolated and tested with monoclonal antibodies. The ratio T4/T8 did not show any significant difference from that found in the unfractionated lymphocyte populations. The results indicate a decrease in the T4 subset in relation to T8 irrespective of disease stage. (no Refs)

16. SERIAL STUDIES OF IN VITRO LYMPHOCYTE TRANSFORMATION BEFORE AND DURING CHEMOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (MEETING ABSTRACT).

Konjevic G
No affiliation given
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Lymphocyte transformation with PHA (phytohemagglutinin) was measured morphologically and by incorporation of 3H-Thymidine to assess cell-mediated immunity in 22 children with ALL. Median follow-up time was 1.5 years (range 3 to 36 months). Before therapy, the majority of children had a significant decrease in both tests. In the initial period the tests proved to have prognostic value as 5 of 7 children with lowest lymphocyte reactivity had a shorter survival period. The greatest decrease in lymphocyte transformation occurred after 3 months of intensive chemotherapy. During reinduction and maintenance therapy an increase in lymphocyte reactivity appeared, but even this was very significantly below the level for healthy children. From the aspect of the activity of disease we found no significant improval in lymphocyte response during remission while in vitro incorporation of 3H-Thymidine, initially and at relapse, was very significantly increased. Intensive forms of polychemotherapy used to treat ALL caused a significant and prolonged impairement of lymphocyte transformation which strongly correlated with the occurrance of severe infections in these children. (no Refs)

17. NATURAL KILLER LYMPHOCYTE FUNCTION IN CERVICAL CANCER PATIENTS.

Pulay TA, Beneczur M, Varga M
Dept. Gynecology and Obstetrics, Semmelweis Medical Univ., 1088 Budapest, Hungary
Neoplasma; 29(2):237-240 1982

Authors investigated the natural killer and antibody dependent cellular cytotoxicity functions of lymphocytes in cervical cancer patients. According to the results the natural killer function showed remarkable changes related to the extent and the course of the disease. On the contrary, radiation therapy did not influence this function. The antibody dependent cellular cytotoxicity function of the same lymphocytes did not show any alteration under circumstances mentioned above. (Author abstract) (10 Refs)

18. AUGMENTATION OF NATURAL KILLER CELL ACTIVITY AFTER ARTERIAL EMBOLIZATION OF RENAL CARCINOMAS.

Gothlin JH, Bakke A, Haukaas SA, Kalland T
Dept. Diagnostic Radiology, Univ. Bergen Medical Sch., N-5016 Bergen, Norway
Excerpta Med Int Congr Ser; 575:74-76 1982

Natural killer cell (NKC) activity was studied after arterial embolization in 12 patients referred to renal angiography with suspicion of carcinoma and in 2 patients who underwent only angiography. In the two patients no change in NKC-activity was observed. Time dependence of NKC-activation of peripheral blood lymphocytes was investigated in 3/12 patients. NKC-activity was determined immediately prior to embolization and at 24-hr intervals up to 96 hr. Twenty-four hr after embolization a slight increase, and after 48 hr a marked augmentation of NCK-activity was observed. The high levels of activity remained during the time of observation. In all 12 patients the level of NCK-activity at 48 hr was compared to that prior to embolization. Increased NCK-activity was observed in 10/12 patients. Two out of 12 patients had open bicpsies of bone metastases 2 days prior to embolization. The fever that developed in all patients has in most cases not exceeded 38 C and no real hyperthermia thus developed. The mechanism of the embolization-induced NKC-activity is not known. No alteration in the total number of T and B lymphocytes was observed. The augmented NCK-activity may be the result of a general increase in the number of lytic capacity of NCK or merely a redistribution of effector cells to peripheral blood. (no Refs)

19. NATURAL KILLER CELL AND ANTIBODY DEPENDENT CELLULAR CYTOTOXICITY IN HODGKIN'S DISEASE, NON-HODGKIN'S LYMPHOMA AND RENAL TRANSPLANTATION (MEETING ABSTRACT).

Proctor SJ, Dickinson AM, George S, Jacobs E
Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

The present study was designed to assess the effect of Imuran and Prednisone on cell cytotoxicity in an NK (Natural Killer cell) and ADCC (antibody dependent cell cytotoxicity) assay in transplant patients with Hodgkin's disease and non-Hodgkin's lymphoma. Target cell for the NK assay was K562 erythroleukemia cell line. Chang liver cells were used as targets in the ADCC assay. The cytotoxicity testing was performed on the separated peripheral blood lymphocytes and overnight cultures from affected lymph nodes in a small group of patients with Hodgkin's disease and non-Hodgkin's lymphoma. The results indicate a gross suppression of NK and ADCC activity in transplant patients (mean NK 12%, mean ADCC 8%, Cr release in 4 hour assay) in comparison with normals (mean NK normal 40%, mean ADCC normal 38%). NK and ADCC activity was normal in peripheral blood in Hodgkin's patients and those patients with non-Hodgkin's lymphoma showing complete response to treatment. In a group of 10 high grade NHL patients (patients dying less than one year from diagnosis) NK and ADCC activity was also significantly reduced (mean NK 22%, mean ADCC 15%). In suspensions from lymph nodes activity at a low level was seen in two patients with Hodgkin's disease demonstrating atypical clinical and cytological features. (1 Ref)

20. GENERATION OF SUPPRESSOR CELLS FOR NATURAL KILLER CELL ACTIVITY CANCER PATIENTS BY SURGERY (MEETING ABSTRACT).

Uchida A, Colot M, Micksche M
Institute for Cancer Research, University of Vienna, Vienna, Austria
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

As surgery often resulus in an increase incidence of metastases, it is important to know the effects of surgery on natural killer (NK) cell activity and its regulatory mechanism in cancer patients. NK activity against K562 cells determined in a 4-h chromium release assay of untreated patients was comparable to that of normal controls. After surgery blood NK activity significantly depressed, while the number of large granular lymphocytes was not reduced. When postoperative lymphocytes were depleted of monocytes and cultured for 24h, they showed an increase in NK activity. However, the mere addition of blood monocytes to cytotoxicity assays did not inhibit NK activity. Twenty-four hour preculture of NK cells and postoperative monocytes suppressed NK activity. The monocytes also suppressed the enhancement of NK activity by interferon. These results suggest that postoperative monocytes inhibit maintenance and development, but no effector phase, of NK cells. After contact with suppressor monocytes, NK cells changed their form from irregular motile one to roundresting one and lost their active motility, which could be one mechanism of NK suppression since the motility of NK cells is an important step to NK-cell-mediated cytolysis. This was confirmed by using a new agarose microdroplet assay in which NK cells migrated from an agarose droplet toward target cells in medium and killed them. OK-432, a streptococcal preparation, reduced the suppressor activity of monocytes both in vivo and in vitro. (no Refs)

21. INDUCED CYTOTOXIC ACTIVITY IN HODGKIN'S AND NON-HODGKIN'S LYMPHOMA (MEETING ABSTRACT).

Jones DB, Higginson K, Wright DH
University Department of Pathology, General Hospital, Southampton S09 4XY, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

The data presented represents a preliminary study of natural killer activity inducible in mononuclear cells prepared from tissue biopsies of Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). Mononuclear cell preparations from 15 HD spleens showed a significant increase in native NK activity when compared with cells from 20 control spleens. NK activity was low or absent in 7 spleen cell preparations from patients with NHL. This low activity could not be explained by dilution of effector cells by tumor, or by the absence of T lymphocytes. The induction of cytotoxicity by coculture with mitomycin C treated lymphoblastoid cells; polyclonal lymphocyte activators which induce NK like effectors via the induction of interferon synthesis gave comparable results. Cells from HD spleen were easily inducible to high levels of activity against K562 target cells. NHL tissue cells gave levels of induced cytotoxicity which fell below those observed with normal spleen cells. The induction results suggest that qualitative or quantitative differences exist between the spleen cell populations in HD and NHL which account for the differing response of polyclonal T cell activation. Individual HD spleens also produce significant killing over 5 days in control culture with non-mitogenic human AB serum. (1 Ref)

22. MONOCYTE-MEDIATED CYTOSTATIS AND SUPPRESSION IN PATIENTS WITH GASTRIC CANCER (MEETING ABSTRACT).

Mytar B, Uracz W, Czupryna A, Zembala M
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Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

The ability of monocytes from patients with gastrointestinal cancer to inhibit tumor cell growth L1210 and K562 and suppress PHA-induced lymphocyte response in vitro was assessed. To exclude the effects of K, NK or T cells, monocyte-enriched adherent cells (AC) were used as effectors. AC from cancer patients showed an increased ability to inhibit the growth of L1210 cell line while the growth inhibition of K562 cell line was similar in control and patient's group. No cytolysis of both cell lines was observed. The increased cytostatic activity of patients monocytes against L1210 cell line was associated with their suppressor activity assessed by inhibition of PHA-induced normal lymphocyte response. This suggests that suppressor monocytes are also able to arrest tumor cell growth in vitro. Monocytes of some cancer patients possess an increased 'functional expression of Fc receptor' and NBT reduction ability which may indicate their 'activation' in the course of disease. Such 'activated' monocytes inhibited mitogen-induced normal lymphocyte response and arrested the growth of L1210 cell line, while monocytes with normal NBT values and Fc receptor expression caused neither inhibition nor suppression. These observations suggest that 'activated' monocytes of some gastric patients may play a role of suppressor cells and simultaneously exert anti-tumor effect in vitro. (2 Refs)

23. SUPPRESSION OF NORMAL LYMPHOCYTE ACTIVATION BY BRAIN TUMOR CYST FLUIDS (MEETING ABSTRACT).

Neuwelt EA, Kikuchi K, Hill SA
No affiliation given
Neurology; 38(4,part2):A146 1982

The present investigation was conducted to examine the effects upon normal lymphocyte activation of the addition of brain tumor cyst fluid or CSF (cerebrospinal fluid) in an in vitro culture system. It was felt that factors present in these fluids may play a role in the local and systemic immunosuppression in tumor-harboring patients. We have evaluated the effects of the cyst fluid and CSF from eight patients with brain tumors (one astrocytoma, five glioblastoma multiforme, one medulloblastoma, and one microglioma) on mitogen-stimulated lymphocyte function as measured by 3H-thymidine incorporation, cell size distribution and cellular proliferation. Lymphocytes from normal volunteers were incubated for 90 hours in culture medium with 10% pooled human serum, mitogens (phytohemagglutinin: PHA, concanavalin A: con A, and pokeweed mitogen: PWM), and a range of volumes of each cyst fluid or CSF sample. Significant suppression of mitogen-induced blastogenesis of the lymphocytes was demonstrated in the presence of 5 out of 6 cyst fluids, and mitogen response was not affected by the addition of the patients' CSF to the culture medium. The suppression of lymphocyte activation by cyst fluid increased in proportion to the concentration of the cyst fluid. These studies suggest that brain tumor cells locally produce suppressive factors capable of inhibiting lymphocyte activation, but these factors are not present in CSF in sufficient concentrations to affect lymphocyte activation in this system. (no Refs)

24. THE RELATIONSHIP BETWEEN NATURAL CELL-MEDIATED CYTOTOXICITY (NCMC) AND SERUM FACTORS IN ACUTE LEUKEMIA AND OTHER MALIGNANT DISEASES.

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Onkologie; 4(1):22-23,26-28 1981

Natural cell-mediated cytotoxicity (NCMC) of human peripheral lymphocytes against allogeneic tumor line (K-562) was substantially increased by the AB serum. Dialysis, as well as Sephadex G-200 gel filtration of AB serum revealed that the immunoglobulin containing fraction was the responsible factor for the increase. Results suggest the involvement of antibodies in NCMC. Autologous and allogeneic serum of patients with gynecological carcinoma inhibited (10-64%) and/or stimulated (10-250%) the NCMC activity in the patients. Residual NCMC activity exceeding 20% has been present after the trypsin digestion in serum free medium of effector lymphocytes. A similar 20% residual activity has been observed after the addition of anti-immunoglobulin and antigen-antibody complexes, respectively. Our findings suggested the role of antibodies and serum factors in natural killer activity. Nonetheless other mechanisms resistant to trypsin treatment and of a certain specificity to tumor cells may not be excluded. (Author abstract) (25 Refs) (In GER)

25. MONOCYTE MIGRATION IN PATIENTS WITH ADVANCED LYMPHOPROLIFERATIVE DISORDERS AND LEUKAEMIAS (MEETING ABSTRACT).

Graubner M, Gotz J, Heidloff M
Zentrum Innere Medizin der Justus-Liebig-Universitat Giessen, Giessen, W. Germany
9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

The migration of monocytes was studied in 18 patients with Non-Hodgkin's lymphoma (NHL), stage III and IV, 16 pat (patients) with Hodgkin's disease (HD), stage IV, 10 pat with acute monocytic or myelomonocytic leukemia (AMoL/AMML, 10 pat with acute lymphocytic leukemia (ALL), 9 pat with chronic granulocytic leukemia (CGL) and - in addition - the migration of hairy-cells in 9 pat with hairy-cell-leukemia. The Boyden-technique was used in the modification according to Wilkinson. Cell response was evaluated according to the method of Zigmond and Hirsch. We found a significant reduction in monocyte migration compared to normal monocytes: mean: 61.4% in AMoL/AMML and 77.7% in CGL. The other mean values were in between this range: NHL: 64.4%, HD: 65.9%, ALL: 66.4%. Monoblasts were able to migrate, but this capacity was reduced too. Hairy-cells showed no migration. Heavily impaired migration was seen in pat with grossly advanced Hodgkin's disease and after cytotoxic therapy. The results demonstrate a cellular defect of monocyte migration in these diseases which may play a role in the increased susceptibility to infection in these patients. The absent migration of hairy-cells is a further argument against their monocytic nature. (no Refs)

26. PREOPERATIVE AND POSTOPERATIVE REACTIVITY OF BREAST CANCER PATIENTS AGAINST TUMOR-ASSOCIATED ANTIGENS AND HEP IN THE MACROPHAGE-ELECTROPHORETIC-MOBILITY (MEM) TEST.

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Arch Geschwulstforsch; 52(6):469-478 1982

Fifty women, including 27 with breast cancer (BC) and 23 with benign diseases of the breast, were testes preoperatively by the macrophage-electrophoretic-mobility (MEM) test. Patients with BC included five with a second BC occurring several yr after ablation of the contralateral breast. Patients with benign diseases included 21 with benign tumors (16 fibrocystic mastopathies, 2 fibroadenomas, 1 foam-cell granuloma, 1 intracanalicular papilloma, and 1 lipoma). Patients with BC were tested 4-7 days, 5-8 wk, and 11-20 wk postoperatively. In all tests, MEM tests were conducted in the presence of human encephalitogenic protein (HEP), 3 M KCl extract of BC tissue, or 3 M KCl extract of renal carcinoma (RC). A total of 289 tests were conducted on 102 blood samples from 50 patients.

Preoperative diagnosis by the MEM test had an accuracy of 89%, a sensitivity of 86%, and a selectivity of 91% with BC extract; with HEP the accuracy was 86%, the sensitivity 75%, and the selectivity 95%. With RC extract, positive results were obtained in only 3% of tests; the selectivity was 97%, indicating that the MEM test is organ-specific. In BC patients, reactivity to HEP and BC extract was not immediately affected by surgery. Reactivity declined sharply 5-8 wk after surgery. In some patients reactivity later increased, suggesting a recurrence of BC. Inhibition of lymphocytic migration showed two nonoverlapping groups, one with values near 0% and one with values near 10%. The MEM test using HEP or BC extract as the antigen is evidently useful for differentiation of benign and malignant breast disease and for follow-up of BC. (32 Refs) (In GER)

27. IN VITRO PRODUCTION OF LEUCOCYTE MIGRATION INHIBITORY FACTOR BY LYMPHOCYTES IN EXUDATIVE PLEURAL EFFUSIONS.

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J Clin Lab Immunol; 8(2):107-111 1982

Leukocyte migration inhibitory factor (LIF) production was investigated in pleural effusions of 19 patients using an indirect WBC migration inhibition test. Nine patients (62-83 yr old, av 70 yr) had a malignant, five (25-65 yr old, av 43 yr) a tuberculous, and five (39-64 yr old, av 43 yr) a nonspecific (most probably infectious), pleural effusion. Purified protein derivative (PPD) stimulated LIF production from 9 patients to a greater extent than in 10 patients who had a negative PPD skin test. Both, stimulated and unstimulated LIF production by peripheral blood and pleural fluid lymphocytes varied widely within the patient groups. LIF response to stimulation with leukoagglutinin (LA) was significantly greater in patients with benign disease. LA induced a significantly lower LIF response in pleural fluid than in peripheral blood of patients with malignant pleural effusion. Pleural fluid lymphocytes from four patients with malignant effusion produced LIF spontaneously. In patients with tuberculous pleural effusions, the stimulated and unstimulated LIF production by peripheral blood lymphocytes was equal to that of pleural fluid lymphocytes. Pleural fluid lymphocytes from patients with nonspecific pleural effusion did not produce LIF spontaneously, but responded to LA and PPD stimulation. LA induced a significantly higher LIF production in pleural fluid lymphocytes than in peripheral blood lymphocytes. Patients with pleural effusion from lung carcinoma and with spontaneous LIF production lived for more than 6 mo after thoracentesis, whereas patients from the same malignancy group without spontaneous LIF production died within 3 mo after thoracentesis. (31 Refs)

28. THE IN VIVO EFFECT OF A THYMIC FACTOR (THYMOSTIMULIN) ON IMMUNOLOGIC PARAMETERS OF PATIENTS WITH UNTREATED HODGKIN'S DISEASE.

Martelli MF, Velardi A, Rambotti P, Cernetti C, Bertotto A, Spinozzi F, Bracaglia AM, Falini B, Davis S
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Cancer; 50(3):490-497 1982

The in vivo effect of a calf thymus extract (thymostimulin, TS) on the E-rosetting capacity, PHA blastogenic response, serum migration inhibitory activity (LIF) and skin reactivity to recall antigens was evaluated in 19 untreated patients with Hodgkin's disease. In patients the mean percentage of peripheral blood lymphocytes forming E-rosettes increased from 47 to 55.7% (p less than or equal to 0.001; normal: 58.9). The mean PHA stimulation index rose with all three concentrations tested but did not reach normal values. Serum LIF was positive in only one patient prior to treatment with a total patient mean LIF of 1.03. Nine patients developed a positive LIF following treatment with a mean LIF for all patients of 0.75 (p less than or equal to 0.005). Skin tests were positive in 10 patients (52.6%) prior to therapy and 18 patients following therapy (94.7%; p less than or equal to 0.05). Thymostimulin, in vivo, appears to return immunologic competency to a population of untreated patients with Hodgkin's disease. (Author abstract) (74 Refs)

29. REDUCTION OF SUPPRESSOR CELL ACTIVITY IN PATIENTS WITH HODGKIN'S DISEASE TREATED WITH INDOMETHACIN (MEETING ABSTRACT).

Minassian AA, Sorokin EN
Laboratory of Clinical Immunology, Cancer Research Center, Moscow 111487, USSR
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Fourteen previously untreated patients with Hodgkin's disease were treated with indomethacin, 75-150 mg/daily, 7-14 days. Suppressor activity and response to phytohemagglutinin (PHA) of peripheral blood mononuclear cells were determined before and after treatment. Forty healthy blood donors served as controls. The suppressor cell activity was measured by determining the ability of Mitomycin-treated mononuclear cells from patients and controls to suppress the in vitro response of responder cells to PHA. Mononuclear cells from one healthy donor were store in liquid nitrogen for use as responder cells. In patients with Hodgkin's disease before treatment the mean suppressor cell activity was significantly higher than in controls. PHA responses were significantly deppressed. After treatment with indomethacin the suppressor cell activity was dramatically decreased. PHA responses were slightly elevated after treatment the Hodgkin's disease patients with indomethacin. Reduction of lymph nodes after treatment with indomethacin was observed in 7 out of 14 patiens. (no Refs)

30. CLINICAL APPROACH TO INFECTION IN THE COMPROMISED HOST.

Rubin RH, Young LS
Infectious Disease and Transplantation Units, Massachusetts General Hosp., Boston, MA, 02115
Clinical Approach to Infection in the Compromised Host. New York, Plenum Medical Book Company, 653 pp., 1981.

A practical guide to patient management in the immunosuppressed host based upon available firm scientific data and on art and judgement of medicine when such data was unavailable is presented. The infections themselves, the potential therapeutic modalities, the clinical settings in which they occur, and the occurrence of such infections are discussed. Epidemiology and prevention of infection in the compromised host (CH), defects in host defense mechanisms, fever and septicemia, etiology and management of the compromised patient with fever and pulmonary infiltrates, CNS infections, fungal infections, mycobacterial and nocardial infections, parasitic disease, Legionnaires' disease, viral hepatitis, and herpes group virus (including Epstein-Barr) infections in CH are discussed. Infections complicating congenital immunodeficiency syndromes, management of infections in leukemia and lymphoma, infection complicating bone marrow transplantation, infection in the renal transplant patient, and surgical aspectes of infection in the CH are described. The immunocompromised patient lacks one or more components of the antimicrobial defense system. Abnormal host disease may result either from disease or from attempts to eradicate disease. Disorders of cell-mediated immunity have long been associated with herpesvirus infection. Such infections may be primary or may result from reactivation of latent virus. (1966 Refs)

31. INTERFERON.

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Mikrobiologiai Intezet, Szededi Orvostudomanyi Egyetem, Szeged, Hungary
Orv Hetil; 123(24):1471-1477 1982

Studies on the nature, mechanism, and antiviral properties of interferon are reviewed. Interferon inhibits the proliferation of tumor cells directly and may protect the host from tumor cells through antibody-dependent cytotoxicity and stimulation of natural killer cells and of phagocytosis. Interferon has been used more or less successfully in the treatment of patients with osteogenic sarcoma, laryngeal papilloma, Hodgkin's disease, breast cancer, and leukemia. However, the trials have covered mostly small numbers of patients without adequate controls. (83 Refs) (In HUN)

32. MANAGEMENT OF ADVANCED HODGKIN'S DISEASE IN REMISSION.

Kiener P, Hausner P, Donner L
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Folia Haematol (Leipz); 109(2):213-217 1982

Patients with Hodgkin's disease (Stage IIIB and IV) after being rendered disease-free with combination chemotherapy, were alternatively allocated to either a group receiving levamisole treatment (Decaris) or to a control group receiving no further therapy until there was evidence of recurrent disease. Laboratory examinations showed that impaired cell mediated immune responses found after termination of intensive chemotherapy were favorably influenced by levamisole treatment. In addition, the duration of remission seems to be longer in the levamisole treated group, although the limited number of patients in the study do not allow a definite conclusion to be drawn. (Author abstract) (14 Refs)

33. STUDIES OF MONOCYTOPOIESIS IN PATIENTS WITH MALIGNANT DISEASE AND AFTER IMMUNOSTIMULATION WITH BCG, USING 3H-THYMIDINE AS A DNA LABEL.

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Nuklearmedizin; 21(2):49-52,53-54 1982

Proliferation of monocytes was studied in 69 patients with malignant diseases. Patients included 8 with Hodgkin's disease (HD), 15 with non-Hodgkin's lymphoma (NHL), 9 with mycosis fungoides (MF), 10 with breast cancer (BC), and 27 with malignant melanoma (MM). Monocytic proliferation was measured in all patients prior to treatment. 3H-Thymidine was used as a DNA label. Monocytic proliferation was also measured in eight patients with BC and 8 with MM after two and four immunostimulations with BCG and in 27 patients with MM at 4-wk intervals before BCG immunostimulation for a period of up to 10 mo. Patients with each type of malignancy showed increased proliferation before treatment. All patients with HD showed increases in the fraction of monocytes in the bone marrow (BMM: 6.4%, compared with 2.8% in normal individuals), thymidine labeling index (TLI: 20.0 vs 12.1), and fraction of peripheral blood monocytes (PBM: 617 vs 325). Among 15 patients with NHL, BMM was 3.3%; TLI in the bone marrow was below normal in 6 patients, normal in 5, and above normal in 3. In patients with MF, BMM was 4.8%, TLI 32.0, and PBM 738. In patients with MM, BMM was 3.7%, TLI 14.9, and PBM 398. In patients with BC, BMM was 4.6%, TLI 12.0, and PBM 569. Postoperative prophylactic BCG stimulation increased the proliferation of monocytes. Proliferation returned to normal, however, 4-6 mo after the start of BCG therapy. Monocytopoiesis is evidently stimulated by malignancies. BCG increases monocytopoiesis only during mo 1 of therapy. (22 Refs) (In GER)

34. CHEMOTAXIS OF BLOOD MONOCYTES IN PATIENTS WITH SMALL CELL ANAPLASTIC CARCINOMA OF THE LUNG (MEETING ABSTRACT).

Nielsen H, Dombernowsky P
Medical Department C, Bispebjerg Hospital, DK-2400 Copenhagen, Denmark
9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

A prerequisite in the macrophage - tumor interaction is the chemotactic locomotion of monocytes from the blood stream towards a focus of neoplastic cells in the tissue. In contrast to other histologic types of lung cancer the small cell anaplastic carcinoma is scarcely infiltrated with mononuclear cells. With a modified Boyden chamber technique we studied the monocyte chemotactic responsiveness (MCR) in 14 patients with small cell anaplastic carcinoma of the lung before any treatment and 6 months after combination chemotherapy was initiated. In addition 28 healthy (control) subjects were studied. The MCR was 23 monocytes/high power field (HPF) in the controls and 13 monocytes/HPF in the patient group before treatment. The MCR in the patient group after chemotherapy was 24 monocytes/HPF, and this does not differ significantly from the control group. Moreover, casein incubated with patient plasma had 75% of normal activity, while casein incubated with control plasma had 121% of normal activity. This difference is highly significant. This chemotactic factor inhibitor (CFI) activity diminished after therapy as casein incubated with plasma from patients after therapy had 98% of normal activity. The observation that the depressed MCR normalized and CFI activity decreased after chemotherapy had diminished the tumor burden supports the concept that the tumor produces factors which counterattack the accumulation of mononuclear phagocytes in tumor sites. (no Refs)

35. INHIBITORS OF MONOCYTE RESPONSES TO CHEMOTAXINS ARE ASSOCIATED WITH HUMAN NEOPLASMS (MEETING ABSTRACT).

Synderman B, Cianciolo G
Howard Hughes Medical Institute, Duke University, Durham, NC
9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

We examined the effects of cancerous effusions on a newly developed assay of monocyte function. This assay quantifies monocyte polarization, ie, the rapid alteration in the cell's morphology from round to a triangular 'motile' configuration in response to chemoattractants. All 17 malignant effusions tested, representing 15 tumor types, inhibited monocyte polarization induced by the chemoattractant N-formyl-methionyl-leucylphenylalanine by 45-89% in binded assays. None of 17 benign effusions significantly inhibited polarization (0-15%). Dilutions of cancerous effusions as low as 1:200 produced inhibition that was time, temperature, and dose dependent. Monocyte polarization induced by activated serum or by chemotactic lymphokine was also blocked by cancerous effusions. The inhibitory activity affected the monocyte directly, and did not destroy the chemoattractant. In contrast to its effects on monocytes, the inhibitors in cancerous effusions did not affect the polarization of granulocytes to chemotactic factors. High pressure liquid chromatography of five cancerous fluids revealed three peaks of monocyte inhibitory activity: greater than or equal to 200,000, 46,000, and 21,000 daltons. Fractionation of noncancerous effusions disclosed only small amounts of the highest molecular weight inhibitory activity. The inhibitory activity in cancerous effusions was heat stabie (56C, 30 min), trypsin sensitive, and could be absorbed by three different monoclonal antibodies reactive to P15(E), a structural component of oncogenic type C retroviruses. In contrast, six monoclonal antibodies with other specificities had no effect on the inhibitors or polarization. Human cancerous effusions thus contain novel proteins that are potent inhibitors of monocyte function. (no Refs)

36. ALTERED ENZYME ACTIVITY OF MONOCYTES AND LYMPHOCYTES IN PATIENTS WITH HODGKIN'S DISEASE (MEETING ABSTRACT).

de Mulder P, Van Rennes H, De Pauw B, Wagener D, Mier P, Haanen C

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Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

In a recent study we demonstrated a significantly enhanced cytotoxic activity of monocytes in patients with Hodgkin's disease (HD) in comparison to normal controls. In view of this increased function we studied five key-enzymes in monocytes isolated with cell-scatter-monitored counterflow centrifugation. The enzymes measured were: one of the glycolytic pathway, phosphoglucose isomerase; one of the hexose monophosphate shunt, glucose-6-phosphate dehydrogenase; the krebs cycle enzyme, isocitrate dehydrogenase; and two lysozomal enzymes, n-acetyl glucosaminidase and acid phosphatase. Additionally these enzymes were studied in concomittant isolated lymphocytes. We investigated 10 patients and 10 normal controls. Using appropriate substrates the fluorescent end products were measured with a fluorometric micro assay. The purity of the monocytes of both patients and normal controls averaged 90%, with a recovery of 80%, the lymphocyte purity was 98%. We found a significantly increased glucose-6-phosphate dehydrogenase activity in monocytes from patients with Hodgkin's disease in comparison to normal controls, for the other enzymes no clear differences were observed. In the lymphocytes both glucose-6-phosphate dehydrogenase and phosphoglucose isomerase were significantly increased. Our results indicate an increased hexose monophosphate shunt activity in monocytes from patients with HD. In the lymphocytes both the glycolytis and hexose monophosphate shunt activity was enhanced. (no Refs)

37. STUDIES ON THE EFFECT OF CARCINOEMBRYONIC ANTIGEN (CEA) ON LEUCOCYTE MIGRATION INHIBITION IN PATIENTS WITH COLORECTAL CANCER (MEETING ABSTRACT).

Kojima O, Uehara Y, Kurimoto T, Yamane T, Kasuga M, Watanabe S, Nishioka B, Majima S

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IXth Biennial Congress of the International Society of University Colon and Rectal Surgeons, June 6-10, 1982, Munich, W. Germany. Society of University Colon and Rectal Surgeons 175 pp., 1982.

At the 8th Congress of ISUCRS, we reported that the leukocyte migration inhibition test (LMI) detected cell-mediated immunity against tumor-associated antigens of colorectal cancer. Leukocyte from patients with colonic or gastric as well as from healthy controls were tested by the LMI (Clausen Method)using allogenic 3M KCl extracts of colonic cancer tissues. The normal range of migration index (MI) was found to be i0.83 and 1.19i by calculating the mean MI e 2SD of ten volunteers with cancer extracts. MIs out of this range were considered to be pathologic. In the LMI, a pathologic MI was found in 48% of tests on 91 colorectal cancer patients. This number was significantly higher than those of tests on other groups of patients. The primary purpose of this study was to determine whether the CEA concentration influenced the LMI reactivity in colorectal cancer patients. According to CEA concentration, colonic cancer extracts were classified into two groups (ie a low CEA group with a concentration of 50 ng/mg protein or less and a high CEA group with a concentration of more than 50 ng/mg protein). In the LMI with extracts from the low CEA groups, 42% of tests showed a pathologic MI. With extracts from the high CEA group, 48% of tests showed a pathologic MI. Colonic cancer extracts having either a high or a low CEA concentration did not differ in LMI reactivity. In addition, a pathologic MI was found in 44% of tests on colorectal cancer patients low plasma CEA levels (0-5 ng/ml) and in 48% of tests on patients with high plasma CEA levels (i5 ng/ml). In conclusion, variations in the CEA concentration of cancer extracts and plasma CEA levels do not influence LMI reactivity in colorectal cancer patients. (no Refs)

38. ASBESTOS RELATED CHANGES IN PULMONARY AND SYSTEMIC IMMUNE RESPONSES - EARLY ENHANCEMENT FOLLOWED BY INHIBITION.

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Clin Exp Immunol; 49(2):426-432 1982

We recently developed an animal model in order to study the pulmonary and systemic reactions following exposure to environmental pollutants. In this model, conscious sheep received repeated intratracheal instillations of a suspension of 0 (controls), 2 mg (low dose) or 128 mg (high dose) of chrysotile asbestos fibers over a 12-mo period. A significant dose-dependent enhancement in proliferative responses of pulmonary free airway cells (FAC) to four mitogens was observed after a first instillation. A somewhat weaker stimulation was also observed in peripheral blood mononuclear leukocytes (PBML). At 6 mo, the high dose animals no longer displayed the dose-dependent enhancement of FAC responses and manifested actual depression of PBML responses. At 12 mo, all asbestos exposed animals showed impaired responses of FAC, whereas only the PBML of high dose animals were showing such an impairment. These data suggest that asbestos exposure has a dose-dependent initial enhancement of local pulmonary as well as systemic responses to mitogens while prolonged exposure and higher doses can subsequently lead to a relative depression of local and systemic cellular immune activity. Although responsive early after asbestos exposure, systemic immunity appears to lag behind local immunity in the late depressive effect of asbestos fibers on mitogen responsiveness. In addition to these cell-directed effects serum factors seem to play an inhibitory role in lymphocyte responses to mitogens in animals repeatedly exposed to asbestos. (Author abstract) (25 Refs)

39. SUPPRESSION OF LYMPHOCYTE RESPONSES BY MONOCYTES WITH UNTREATED AND TREATED MULTIPLE MYELOMA.

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Blood; 60(2):316-322 1982

Studies were performed on 15 untreated and 14 treated patients with multiple myeloma. The monocyte content was normal in blood but elevated in mononuclear leukocytes (MNL) from treated but not untreated patients (p less than 0.001). This correlated with the severity of lymphopenia in blood (p less than 0.01). Three patterns of immunoglobulin (Ig) synthesis emerged. (1) Most untreated patients showed normal polyclonal responses to pokeweed mitogen. (2) Of 12 treated patients, the 8 whose MNL included greater than 30% monocytes had subnormal Ig responses to pokeweed mitogen. Ig synthesis increased when adherent cells that suppressed Ig synthesis were depleted. Suppression in vitro bore no relationship to polyclonal immunoglobulin levels in serum. (3) Three patients had early blood invasion by plasmacytoid cells. Their MNL spontaneously released large amounts of the Ig class of their serum gammopathies. Proliferative responses to phytohemagglutinin by MNL from all patients were reduced, in part due to monocytoid cell suppression and in part to intrinsic T-cell hyporesponsiveness. B- and T-cell responses in vitro are sometimes suppressed with myeloma. This is related to elevated monocyte percentages in MNL preparations. This excess of monocytes is a function of lymphopenia secondary to therapy, rather than the primary malignant process itself. No evidence was found that suppression by monocytes is qualitatively altered by myeloma or its treatment. (Author abstract) (33 Refs)

40. CELL-MEDIATED IMMUNITY TO HUMAN ORAL CARCINOMA, AND CROSS-REACTIVITY TO PATIENTS WITH ORAL LEUKOPLAKIA DEMONSTRATED BY THE LEUKOCYTE MIGRATION TEST.

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Allergy; 37(6):429-435 1982

Cell-mediated immunity to human oral neoplasias was studied using WBC from 18 patients with histologically confirmed carcinomas of the oral mucosa and 11 patients with oral leukoplakia. The carcinoma patients included 13 males and 5 females, 45-84 yr old. One patient had a history of penicillin exanthema, and one a history of carcinoma of the common bile duct. Otherwise, none of the patients had any disease affecting the immune system. Fourteen patients had been treated with irradiation and 10 with bleomycin. Leukocyte migration tests (LMCT) were performed 1-9 days after surgery. LMCT were performed using extracts from the 18 tumors and WBC from the patient of origin and an age- and sex-matched control. Normal migration was defined as a migration index (MI) within two standard deviations of the mean value for controls. Significant inhibition was found with WBC from three carcinoma patients; an MI in the low-normal range was found for one patient. None of the carcinoma patients showed stimulation of WBC migration. WBC from the leukoplakia patients were tested against tissue extracts from two of the oral carcinomas and from normal intestine. The MI for the carcinoma extracts were significantly different from those for the intestinal extracts. Findings support the existence of tissue-specific, cell-mediated hypersensitivity to antigens from oral carcinoma and oral leukoplakia. Oral carcinoma and oral leukoplakia may have common antigens. (43 Refs)

41. IMMUNODIAGNOSIS OF PROSTATE CANCER: AN EVALUATION OF CELL-MEDIATED IMMUNITY.

Bhatti RA, Guinan PD, Nagubadi SR, Khin W
Div. Urology, Cook County Hosp., Chicago, IL, 60612
Prostate; 3(4):415-419 1982

Cell-mediated immune reactivity was studied in 342 patients (59-90 yr old) with histologically confirmed diagnosis of adenocarcinoma of the prostate. Among these patients, 69% were in Stage D, 10% were in Stage C, 15% were in Stage B, and 6% were in Stage A. The patients received conventional treatment. Sensitization to tumor-associated antigens was measured by the leukocyte adherence inhibition (LAI) assay. LAI was considered positive if the nonadherence was of WBC was 15% or more. Of 342 patients, 276 were true positives, while the remaining 66 patients were classified as false negatives. Of 192 control subjects, 85 gave nonadherence of 15% or more; these were shown to be false positives. These results indicate that the sensitivity and specificity of the LAI assay was 81% and 56%, respectively. The sensitivity of the LAI assay was the highest in patients with Stage B cancer of the prostate (87%) and the lowest in those with Stage C cancer. (17 Refs)

42. IMMUNOLOGICAL MONITORING IN LUNG CANCER: USE OF THE LEUKOCYTE MIGRATION INHIBITION ASSAY.

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Haematologia (Budap); 15(1):111-125 1982

The indirect agarose microdroplet leukocyte migration inhibition assay was used to detect and monitor an immunity blocking factor thought to be cell-mediated in the serum of lung cancer patients before and after chemotherapy. Using the direct technique, alterations in cell-mediated immunity were observed. It is suggested that in vitro investigations of cell-mediated immunity which do not take into account the role of serum or serum factors may be inadequate. (39 Refs)

43. ACQUIRED IMMUNODEFICIENCY AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Geerling J
Afdeling Inwendige Ziekten, Slotervaartziekenhuis, Amsterdam, The Netherlands
Ned Tijdschr Geneeskd; 126(14):631-633 1982

Recent studies on the sudden increase in the incidence of Kaposi's sarcoma mostly in homosexual men abusing drugs are reviewed. The new syndrome is characterized by very poor prognosis and high incidence of infectious disease indicative of impaired cell-mediated immunity. Kaposi's sarcoma is believed to be of viral etiology. Human leukocyte antigen Dr 5 was found in 10/12 patients examined, while the frequency of this antigen is only 12% in the general population. (7 Refs) (In DUT)

44. ROLE OF NONSPECIFIC IMMUNOLOGICAL METHODS IN THE EXAMINATION OF PATIENTS WITH CARCINOMAS OF THE HEAD AND NECK REGION.

Kovesi G, Fekete B

Szajsebeszeti es Fogaszati Klinika, Semmelweis Orvostudomanyi Egyetm, Budapest, Hungary

Magy Onkol; 26(2):186-190 1982

The nonspecific immunity was studied in 20 patients (16 men and 4 women, 44-73 yr old, av age 60.3 yr) with carcinomas of the head and neck region and in 15 controls (av age 57.7 yr). The tests included skin tests with Purified Protein Derivative (PPD), Candida antigen and phytohemagglutinin, as well as active (EA) and total (ET) rosette tests. Keratinizing carcinoma was diagnosed in most patients. Four patients were in Stage I, four in II, three in III and nine in IV. Lymph node metastases were present in 16/20 patients, distant metastases in 4/16. The hyperemic reactions to all three antigens used in the skin tests were significantly more intense in the controls than in the patients (p less than 0.001). The induration reaction to Candida antigen and PPD was insignificantly more intense in the controls than in the patients. Both the EA and ET rosette counts were found to decrease with progression of the tumor, while the rosette counts were within normal limits in the controls. The rosette counts were still within normal limits in Stage I. The correlation factors for tumor stage on one hand and the EA and ET rosette counts, on the other hand, were-0.95 and-0.97, respectively. No significant differences were found in the B cell counts between the patients and controls, even though an insignificant increase in the B cell count was observed in tumor Stage III and IV. Good correlation was found between the in vitro and in vivo test results. (27 Refs) (In HUN)

45. THE EFFECT OF CHEMOTHERAPY AND RADIATION THERAPY ON CELLULAR IMMUNE REACTIONS IN PATIENTS WITH MAMMARY CARCINOMA (MEETING ABSTRACT).

Hadjikirove M, Boeva M, Dontchev T

Institute of Oncology, Sofia, Bulgaria

Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Cellular immunity was examined in 171 patients with mammary carcinoma divided into two basic groups: A -69 in stage T1-3N0-2M0; B -102 with metastatic carcinoma. The mean values for E-rosette forming cells in non-treated patients (T1-3N0-2M0) was lower than that of the control group, whereas in patients with metastases (prior to chemotherapy) were considerably lower than that of control group as well as that in patients in stage T1-3N0-2M0. Following preoperative radiation the percentage of E-rosette forming cells was slightly raised as compared with initial level. After chemotherapy (4 therapeutic regimens) a more marked increase was recorded in patients treated with polychemotherapy. A positive correlation was observed between DNCB (dinitrochlorobenzene) test results prior and following cancer treatment and the objective effect on metastases. (no Refs)

EVALUATION OF CELL MEDIATED IMMUNITY IN ANIMALS

46. IMMUNOSUPPRESSION ASSOCIATED WITH SJL/J MURINE LYMPHOMA.

Kumar RK

University of New South Wales, New South Wales, Australia

Diss Abstr Int [B]; 42(11):4368-B 1982

Inbred-strain SJL/J mice develop a lymphoma which is regarded as a possible model of Hodgkin's disease. This study sought to assess the effect of tumor growth on cell-mediated immune function in these animals, to determine whether any demonstrable immunosuppression was cellular or was related to a plasma suppressor factor, and to characterize any such factor. A longitudinal study was devised in which cell-mediated immunological responsiveness of individual animals was assessed in terms of the in vitro proliferative responses of separated peripheral blood mononuclear cells to mitogens, tumor cells and allogeneic cells, both prior to and following the induction of transplanted lymphomata. Tumor-bearing SJL/J mice were shown to develop marked suppression of proliferative responses to the mitogens phytohemagglutinin and concanavalin A. Proliferative responses in mixed lymphocyte-tumor cell culture and mixed lymphocyte culture were also suppressed. There was no deficiency of responder T cells in the separated cell population being tested, nor was suppressor cell activity demonstrable in a variety of in vitro assays. However, plasma from tumor-bearing animals exhibited potent nonspecific immunosuppressive activity. Immunosuppression and the development of plasma suppressive activity were both correlated with tumor growth. Plasma suppressive activity was not due to an intact virus. The suppressor factor appeared to be a non-immunoglobulin protein of molecular weight in the range 68,000-88,000 daltons. Supernatants from short-term cultures of tumorous lymph node cells contained a similar suppressor factor. (no Refs)

47. TRANSFER OF EXPERIMENTAL AUTOIMMUNE OOPHORITIS IN THE RAT (MEETING ABSTRACT).

Vajnstangl M, Jankovic BD

Immunology Research Center, 11221 Belgrade, Yugoslavia

Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Female rats immunized with ovarian tissue develop experimental allergic oophoritis. In this study, experimental autoimmune oophoritis was produced in Lewis rats. The estrus cycle of sensitized rats was characterized by an abnormal cycling pattern and shortening or absence of the estrus phase. When thus immunized animals were mated, almost all of them were found to be infertile as judged by their failure to deliver young. Control animals which received only complete Freund's adjuvant delivered normal litters. The characteristic multifocal accumulation of mononuclear cells in ovaries could be adoptively transferred to isologous recipients by intraperitoneal injections of peripheral blood lymphocytes, lymph node cells, spleen cells, neat immune sera (containing anti-ovarian antibodies), gamma-globulin fraction of immune sera and lymphoid cell suspensions devoid of T or B cells, from donors which developed oophoritis. Peripheral blood lymphocytes were the most active in inducing ovarian lesions in recipient rats. We concluded that both cell-mediated and humoral mechanisms are involved in the pathogenesis of experimental autoimmune oophoritis. (1 Ref)

48. PROTECTION AGAINST A NONIMMUNOGENIC MOUSE LEUKEMIA BY AN IMMUNOGENIC VARIANT OBTAINED BY MUTAGENESIS.

Van Pel A, Boon T
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Proc Natl Acad Sci USA; 79(15):4718-4722 1982

The nonimmunogenic thymic leukemia TH, obtained in mouse strain CBA/Ht, was adapted to culture. By in vitro treatment of a clonal TH cell line with the mutagen N-methyl-N'-nitro-N-nitrosoguanidine, stable variant cell clones (tum-) were obtained that elicited a rejection response in syngeneic mice. Mice that had rejected a tum- variant were partially protected against a challenge with the original tumor. When spleen cells of these animals were restimulated in vitro, cytolytic T cells were obtained that were directed against an antigen present on the original tumor. The existence of these cytolytic effectors was confirmed by clonal analysis of the cytolytic response. No immune protection against TH was observed in mice that had been immunized with irradiated cells of the original TH tumor. These results confirm that tum- variants can elicit a syngeneic rejection response against tumors that are apparently devoid of transplantation immunogenicity. The experimental conditions and the results make it likely but not certain that the tumor-associated antigen detected on leukemia TH was present on the primary tumor. (Author abstract) (26 Refs)

49. LONG-TERM EFFECTS OF IRRADIATION ON CELLULAR COMPOSITION OF LYMPHOID ORGANS AND IMMUNE RESPONSE OF MICE.

Samoilovich MP, Klimovich VB
Central Res. Roentgeno-Radiological Inst., Leningrad, USSR
Radiobiologiia; 22(3):359-364 1982

Relationship between the long-term radiation-induced immunosuppression and the changes in the cellularity of lymphoid organs was studied in male CBA mice subjected to whole-body irradiation (500 rads). The animals were examined within 2-11 mo after irradiation. Irradiation produced marked hypoplasia of the thymus and lymph nodes. The number of T- and B-lymphocytes in the spleen and bone marrow of irradiated mice did not differ from that in nonirradiated controls. Analysis of the immune response after immunization with sheep RBC showed significant decrease of the number of antibody-forming cells in the lymph nodes 8 mo after irradiation. (12 Refs) (In RUS)

50. NATURAL AND INDUCED IMMUNITY TO MOUSE MAMMARY TUMORS AND THE MAMMARY TUMOR VIRUS (MUMTV).

Stutman O
Cellular Immunology Section, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Springer Semin Immunopathol; 4(4):333-372 1982

Information on immune responses in normal and tumor-bearing hosts either against murine mammary tumor virus (MuMTV) antigens or the actual tumors themselves is discussed and correlation with the possible prophylaxis and therapy of tumors in the mouse mammary tumor model system is made. The cell-mediated immune responses (mostly those mediated by T cells), which can be detected in vivo or in vitro either spontaneously or in immunized mice are reviewed in detail. The unique properties of the MuMTV model and in vivo immunologic studies are discussed. Topics discussed include in vitro cytotoxicity and related phenomena (studies using colony-inhibition assays and microcytotoxicity, antigenic complexities of the system) and studies using cell-mediated cytotoxicity assays (specificity and characteristics of the response, in vivo-in vitro discrepancies, serum factors, T cell interactions, suppressor T cells in MTV-positive mice, the effect of thymectomy, in vitro sensitization, natural cell mediated cytotoxicity in MTV-positive mice and horizontal transmission of MuMTV). Adult thymectomy completely abrogated the suppressive activity in the Lyt-23 fraction of MTV-positive cells, but had no effect on the Lyt-1 helper component. These findings may explain the in vivo effects of thymectomy producing a decline of mammary tumors. Thymectomy at 6 days of age produced a significant decrease in tumor incidence, while thymectomy after 30 days of age had no effect on mammary tumor development in C3H/BiUmc virgin females. (247 Refs)

51. IMMUNOLOGICAL ASPECTS OF EXPERIMENTAL BRAIN TUMORS. (REVIEW).

Stavrou D, Bilzer T, Hulten M, Zanker KS, Anzil AP, Haglid KG, Dahme E
Dept. Functional Pathology, Univ. Munich, 8 Koniginstr., 8000 Munich 22, W. Germany
Anticancer Res; 2(3):151-155 1982

Significant findings concerning the expression of glia specific and glioma associated antigens (GAA) in nitrosamide induced neurogenic tumors detected by polyclonal immune response are summarized. Since some brain antigens have been isolated and characterized, and three of them have been suggested to be brain specific, these proteins might be expressed in glioma cells and may be useful as specific markers of brain cells. Nitrosamide induced neurogenic tumors in rats, rabbits, and dogs are capable of synthesizing brain specific antigens in vivo and in vitro. A positive correlation was observed between the demonstrability of glial fibrillary-associated protein and the presence of intermediate filaments in tumorigenic brain cells cultured in vitro. Using cultured glioma cells as targets, specific antibodies were detected in sera of rats which developed brain tumors, by means of an indirect immunofluorescent method and a complement-dependent microcytotoxicity assay. The presence of T-lymphocytes in the cell infiltrates of N-methyl-N-nitrosourea-induced gliomas can be regarded as indirect evidence for the existence of GAA in tumor cells. In support of this interpretation are the findings concerning the presence of a significant number of macrophages within experimental malignant gliomas. (44 Refs)

52. IMPORTANCE OF HELPER T CELLS IN CONFERRING SUCCESSFUL ANTITUMOR IMMUNITY (MEETING ABSTRACT).

Lee FH
University of Southern California Cancer Center, Los Angeles, CA, 90033
Fed Proc; 41(3):417 1982

The type of effector cells in a syngeneic antitumor system was studied using a subline of P815Y mastocytoma cells in DBA/2 mice. In vivo dose response study demonstrated that up to 2 x 10(5) P815Y cells inoculated sc into DBA/2 mice were completely rejected after 30 days. A second injection ip of 10 times more (2 x 10(6)) P815Y cells were also rejected by these mice, indicating the immunological nature of this rejection. Lymphoid cells of lymph nodes (LN), spleens and peritoneal exudates (PE) were prepared from immune mice (1 wk after second challenge) for testing the presence of cytotoxic cells against P815Y tumor, using a 51Cr-release assay. No cytotoxic cells were found in spleens or in pooled axillary and inguinal LN whereas significant cytotoxicity was detected from cells of PE or pooled mesenteric and pancreatic LN. In an adoptive cell transfer experiment, immune cells from these four different sources were each transferred ip (2 x 10(7)/mouse) to a group of DBA/2 mice that had been inoculated sc with a lethal dose (10(6)) of P815Y cells. Surprisingly, only immune spleen cells were able to confer significant protection to mice against P815Y cells. Two out of 6 mice were free of tumor (at 200 days) and the other two enjoyed a long term survival time (98 days) as compared to the controls (35 days). This protective effect of immune spleen cells was completely abrogated after treating them with monoclonal antibodies of rat alpha-mouse Thy 1.2 or alpha-Lyt 1.2 plus rabbit complement, indicating that helper T cells were essential in conferring antitumor immunity to the hosts. (no Refs)

53. INHIBITION OF PRIMARY GROWTH AND METASTASES FROM LEWIS FIBROSARCOMA BY ALLOGENEIC EFFECT FACTOR (AEF) IN VIVO (MEETING ABSTRACT).

Yen-Lieberman B, Chiang T, Deodhar S
Cleveland Clinic Foundation, Cleveland, OH, 44106
Fed Proc; 41(3):408 1982

Soluble helper factor(s) have been reported to generate cytotoxic T lymphocytes against various types to syngeneic and allogeneic tumor cells in vitro. More recently, AEF, a product of secondary in vitro mixed lymphocyte culture, was shown to induce cytotoxic T lymphocytes autonomously against tumor targets. We have studied the ability of AEF given in vivo to suppress the growth and lung metastases of the Lewis T241 fibrosarcoma when transplanted subcutaneously to C57Bl/6 mice. AEF is produced by harvesting supernatants from in vivo alloantigen primed and in vitro alloantigen re-stimulated Balb/c splenic T lymphocytes. Mice were treated with AEF and normal C57Bl/6 supernatants (N-sup) on days-3,-2 and-1 (50 ul/footpad) prior to the tumor transplantation and 5 consecutive days after the tumor implants. AEF, induced in vivo and administered as a cell free supernatant, was able to inhibit primary tumor growth and lung metastases. (no Refs)

54. REGULATION OF ADOPTIVE IMMUNITY BY CYCLOPHOSPHAMIDE-SENSITIVE HOST CELLS (MEETING ABSTRACT).

Kreider JW, Boyer CM, Bartlett GL
The M. S. Hershey Medical Center, Pennsylvania State University, Hershey, PA, 17033
Fed Proc; 41(3):407 1982

Peritoneal exudate T cells (PEC) from rats immune to 13762A rat mammary tumor conferred specific tumor-rejection immunity on normal recipients. The efficiency of systemic adoptive transfer of tumor-rejection immunity with immune PEC was improved by cyclophosphamide (CY) pretreatment of recipients. Optimal potentiation was obtained with a dose of 50 or 100 mg of CY/kg body weight given the day before transfer. CY pretreatment enabled recipients to reject greater numbers (100 times) of tumor cells and inhibited tumor challenge established before systemic adoptive transfer. CY-induced potentiation of adoptive immunity was limited in duration; the potentiation was lost if adoptive transfer did not occur within 4 days of CY-pretreatment. The CY-induced potentiation of systemic transfer of tumor immunity was reversed by iv administered normal spleen or thymus cells. We concluded that CY-sensitive host regulatory cells restricted the expression of adoptive tumor-rejection immunity. Control of the activity of these regulatory cells allows increased efficacy of specific effector T lymphocytes in this system. (no Refs)

55. REGULATION OF ANTIBODY PRODUCTION IN SJL/J MICE BY INJECTION OF GAMMA-IRRADIATED RETICULUM CELL SARCOMA (RCS) (MEETING ABSTRACT).

Katz IR, Bell M, Thorbecke GJ
New York University School of Medicine, New York, NY, 10016
Fed Proc; 41(3):302 1982

Gamma RCS cells induce strong proliferative responses in T cells of syngeneic mice in vitro and in vivo. In an effort to determine whether the response to gamma-RCS affects other immune responses in vivo, the effect of gamma-RCS injection on antibody production to sheep erythrocytes (SE) was determined. Intravenous (iv) injection of 2 x 10(7) gamma-RCS 2 days prior to injection of 10(7) SE (iv day 0) caused enhancement of the direct plaque forming cell response (PFC) from approximately 10,000 to 30,000 PFC/spleen (day 5). In contrast, a similar injection of gamma-RCS on day 0 induced 60-90% suppression of the PFC response. Glutaraldehyde treatment of gamma-RCS (0.1%, 10 min) abolished the enhancing but not the suppressive effect. The suppressive effect of gamma-RCS on the anti-SE response was absent in SJL mice older than 8 months of age. Pretreatment of recipients with 0.5 mg cyclophosphamide (ip) 3 days prior to injection of SE + gamma-RCS prevented suppression. Evidence that suppressor T cells were involved was obtained by studying the effect of antisera to the IJs subregion of H-2. Injection of 0.025 ml of (BI0 x 9R) anti BI0.HTT on day-1 (iv) and day 0 (ip) completely abrogated suppression. Control sera without effect included normal (BI0 x 9R) and SJL as well as anti-Iak sera. It is suggested that the syngeneic MLR to gamma-RCS potentiates the normally occurring suppression of the anti-SE response in vivo. (no Refs)

56. KINETIC STUDIES OF THE IMMUNOPHARMACOLOGIC EFFECTS OF NPT 15392 IN MICE.

Florentin I, Taylor E, Davigny M, Mathe G, Hadden JW
Hopital Paul-Brousse, Institut de Cancerologie et d'Immunogenetique, 14 avenue Paul Vaillant-Couturier, 94804 Villejuif, France
Int J Immunopharmacol; 4(3):225-234 1982

The immunopharmacological activities and kinetics of host response following a single injection of NPT 15392 (9-erythro-(2-hydroxy,3-[9-erythro-(2-hydroxy,3-nonyl) hypoxanthine; ip .1 mg/kg] in normal BALB/c mice were investigated. NPT 15392 modified immune function for at least 14 days after a single administration. Both T-dependent and T-independent antibody production were increased, and differences in the kinetics of the responses implied different mechanisms which might include actions on T helper cells, B cells, and macrophages. NPT 15392 increased the response of spleen cells to stimulation with dextran sulfate, a macrophage-dependent B cell response, and suppressed that to phytohemagglutinin, a macrophage-dependent T-cell response. Cytocidal activity of natural killer cells and T killer cells were increased without affecting antibody-dependent cytotoxicity. NPT 15392 increased the delayed hypersensitivity response to immunization with oxazolone. These results suggest that NPT 15392 may have value in cancer immunotherapy. (12 Refs)

57. IN VITRO AND IN VIVO STUDIES OF CELL-MEDIATED CYTOTOXICITY AGAINST HEPATOMA CELLS MC-29 IN CHICKENS (MEETING ABSTRACT).

Trifonov S, Filchev A
Institute of General and Comparative Pathology, Sofia 1113, Bulgaria
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Cell-mediated cytotoxicity of chicken spleen lymphocytes against tumors cells of transplantable hepatoma Mc-29 has been assessed by the 51Cr releasing method. The following results have been obtained: (a) in 20% of the chickens with hepatoma Mc-29 spleen lymphocytes show cytotoxicity from 5 to 10% and in 33% the cytotoxicity is over 10%; (b) in 50% of the chickens with regressed tumors the cytotoxicity was over 16% and in 25% below 10%; (c) in 44% of the chickens immunized with hepatoma cells the spleen lymphocytes show a cytotoxicity over 10% and in 33% the cytotoxicity is from 5 to 10%; (d) in 20% in the control group the cytotoxicity was to 10% and only in 7% it was over 10%. In the vivo experiments with the WINN test at mixing the spleen lymphocytes with hepatoma cells in ratio 100:1 the following results were obtained: (a) when using lymphocytes from hepatoma Mc-29 bearing chickens a development of tumors approximately in 67% of the recipients was observed, but palpable tumors appeared later in comparison with the controls; (b) tumors developed approximately in 50% of the recipients when using lymphocytes from immunized chickens with hepatoma cells with a similar prolongation of the term of appearance of palpable tumors; (c) at mixing of lymphocytes from healthy chickens with hepatoma cells tumors developed in 80 to 100% of the recipients with palpable tumors appearing a little later when compared to the controls treated with tumor cells only. (no Refs)

58. CYTOTOXICITY OF SPLEEN CELLS AGAINST CELLS OF THE TRANSPLANTABLE MYELOID TUMOUR IN HAMSTERS (MEETING ABSTRACT).

Alexandrov I, Trifonov S, Jakimov M
Institute of General and Comparative Pathology, Sofia 1113, Bulgaria
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

The cell mediated cytotoxicity of spleen cells measured by 51 Cr releasing assays against tumor cells of the transplantable myeloid tumor in hamsters with ratio of lymphocytes to tumor cells 100:1 was determined in vitro as follows: (a) the spleen cells of 15% of the tumor bearing hamsters showed 22% cytotoxicity, 30% of them between 9 and 16%, and the rest below 6%; (b) in 4% of the tumor cell immunized hamsters the spleen cell cytotoxicity was 34.5%, in 30%-14.5% and in 45% the cytotoxicity was under 5%; (c) in 35% of the control hamsters the spleen lymphocytes showed 11.7% cytotoxicity, in 10%-8.5% and in the rest the cytotoxicity was below 5%. (no Refs)

59. METASTATIC GROWTH OF 3-LEWIS LUNG CARCINOMA IN MICE TREATED WITH ALKYL-LYSOPHOSPHOLIPIDS AND LYSOPHOSPHOLIPID-INDUCED PERITONEAL MACROPHAGES.

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Anticancer Res; 1(6):397-402 1981

Action of alkyl-lisophospholipids (ALP) was studied in 3-Lewis lung carcinoma (3-LL) system in syngeneic C57Bl/6 mice. ALP therapy was combined with surgical removal of the primary tumor lesion. Results indicated that sc ALP administered shortly before surgery exhibit an antineoplastic effect. Treatment with ALP injected intracutaneously or sc shortly after tumor removal significantly protected animals from metastasis as determined by the number of surviving mice. Protection was also observed when ALP administration began 3 wk after tumor inoculation and shortly before animals begin to die from metastasis. Ip injection of 2-lysophosphatidylcholine (2-LPC; 1-2 mg/mouse) led to induction of a temporary ascites which contained approx 70% macrophages. Lysophospholipid-induced macrophages exhibited a strong antitumor activity when incubated with cells of 3-LL in vitro. Tumor cell growth inhibition was most effective at pH 6.6-6.8. Iv injection of 2-LPC-induced syngeneic peritoneal macrophages significantly protected mice from 3-LL metastasis. Neither high number of cells (30 x 10(6)) nor repeated macrophages injection improved the results. When macrophages were removed from the peritoneal cell suspension, the remaining lymphocytes and granulocytes had no antimetastatic activity when administered iv. (33 Refs)

60. SYNGENEIC TUMOR IMMUNITY TO BALB/C MKSA-TU5 (TU5) (MEETING ABSTRACT).

Gilbertsen B
University of Wisconsin, Madison, WI, 53706
Fed Proc; 41(3):413 1982

Tumor immunity was studied in BALB/c mice bearing syngeneic, progressively-growing TU5 tumors. Lymphocytes from tumor bearer (TB) mice were restimulated in mixed lymphocyte tumor cell culture (MLTC) with irradiated TU5 and shown to be specifically cytotoxic for chromium-labelled TU5 cells in vitro. Effector cells thus generated prevented tumor growth of TU5 cells in normal BALB/c mice in the Winn neutralization test. Fresh spleen cells from TB mice, TB spleen cells cultured in medium alone, and normal BALB/c lymphocytes stimulated in MLTC with TU5 were inactive in both the cytotoxicity and the Winn assays. VLM-S, an SV40-transformed BALB/c fibroblast, was neither lysed by TB spleen cells restimulated in MLTC with TU5 nor able to block lysis of chromium-labelled TU5 cells by these effectors. VLM-S was, however, lysed by allogeneic effector in cell-mediated lympholysis assays. TUT-3, a spontaneously transformed BALB/c fibroblast, was only weakly lysed by these MLTC-produced TB effectors, but was a potent nonspecific blocker of lysis of TU5 targets as well as of normal allogeneic and syngeneic targets. These data are compatible with the hypothesis that secondary generation of cytotoxicity to TU5 in BALB/c mice is directed towards an antigen(s) qualitatively or quantitatively different from the classically-conceptualized SV40 tumor-specific transplantation antigen. (no Refs)

61. MALIGNANT RABBIT FIBROMA VIRUS: REPORT OF A NEW VIRUS-INDUCED TUMOR CAUSING SECONDARY IMMUNODEFICIENCY (MEETING ABSTRACT).

Strayer DS, Corbeil LB, Cabirac G, Leibowitz J, Skaletsky E, Sell S
University of California, San Diego, La Jolla, CA, 92093
Fed Proc; 41(3):408 1982

Shope fibroma virus (SFV) causes a local, transient proliferation of fibroblasts, which peaks in 10 days and quickly regresses. We have isolated and identified another DNA poxvirus derived from tumors by SFV. This virus, which we call Malignant Rabbit Fibroma Virus (MRF), is antigenically similar to SFV. Immune sera to SFV cross-neutralized MRF and SFV in vitro equally. The clinical syndrome is different: a bizarre fibroblastic proliferation develops locally, followed by histologically identical cutaneous metastases by day 6-7. Simultaneously latent colonization with Pasteurella multocida becomes purulent conjunctivitis and rhinitis. Death soon ensues from respiratory obstruction. Splenic B cell function, measured by anti-Ig blastogenesis, is depressed by day 6 compared to normals and SFV-infected rabbits. Splenic T cell function, measured by con A (concanavalin A) stimulation, and is similarly depressed. Peripheral blood lymphocyte responses are also affected. The depression in immune responsiveness is thus first apparent just before the clinically obvious metastases appear. MRF-induced tumors are possible models for secondary immunologic incompetence and gram-negative infections in oncology. (no Refs)

62. IN VIVO STUDIES OF LOCAL AND SYSTEMIC IMMUNE REACTIONS TO TUMORS.

Mule JJ
University of Washington, Seattle, WA
Diss Abstr Int [B]; 42(6):2301-B 1981

Newly formed long-lived small lymphocytes (LLSL) generated during the immunization of mice to tumor-specific transplantation antigens (TSTA) of syngeneic 3-methylcholanthrene (MCA)-induced sarcomas were labeled with 3H-thymidine. The localization of these labeled cells into tumor implants was then studied. 'Criss-cross' experiments were performed in which MCA-sarcomas with individually distinct TSTA were studied in parallel. When small tumor pieces were implanted into mice whose LLSL has been radiolabled, LLSL selectively localized into tumors to which they were immune. The selective localization of immune LLSL into tumors did not, however, prevent tumor growth. Spleen cells from mice bearing large MCA-induced sarcomas were injected intravenously into mice challenged in the hind footpads with heavily irradiated cells from the same or a different sarcoma. As measured by 3H-thymidine incorporation on day 5 or 6, cellular proliferation in the draining popliteal lymph nodes of these mice was significantly depressed as compared to controls receiving normal spleen cells or medium intravenously. The suppression was mediated by a Qa-1+, Thy-1+ cell that was relatively resistant to treatment with cylophosphamide (100 mg/kg). Following activation by specific tumor antigen (but not with antigen from a different sarcoma), this cell mediated an antigen nonspecific suppression. This nonspecific suppression most likely contributes to the generalized immunologic energy in animals with tumors at a late stage in progression. (no Refs)

63. EFFECTS OF CYCLOPHOSPHAMIDE ON MURINE BONE MARROW AND SPLENIC MEGAKARYOCYTE-CFC, GRANULOCYTE-MACROPHAGE-CFC, AND PERIPHERAL BLOOD CELL LEVELS.

Yeager AM, Levin FC, Levin J
Oncology Center 3-127, Johns Hopkins Hosp., Baltimore, MD, 21205
J Cell Physiol; 112(2):222-228 1982

The effect of cyclophosphamide (CY) on megakaryocytopoiesis in C57BL/6J mice was investigated by serially determining alterations of megakaryocyte colony-forming cells (CFC) derived from the marrow and spleen following ip administration of 200 mg/kg CY. Platelet count showed rebound thrombocytosis after 11 days, while neither hematocrit values nor the total WBC counts exhibited rebound increments during recovery from CY. A decrease in the number of megakaryocyte-CFC (MEG-CFC) was observed in the bone marrow at 24-48 hr after CY, and a rebound increase occurred thereafter and was maximal at 5 days; at 7 days, splenic MEG-CFC were strikingly increased following an initial 5-day period of suppression. Both time and magnitude of the responses to CY of both MEG-CFC and granulocyte-macrophage CFC (GM-CFC) in the mouse marrow were similar. MEG-CFC and GM-CFC of bone marrow and splenic origin differed significantly in their response to CY; in the spleen, both showed similar patterns of recovery after exposure to CY (substantially decreased through day 5) while both had shown maximal rebound increases in the marrow by day 5. The maximal rebound increase in splenic MEG-CFC and GM-CFC occurred by day 7, when marrow-derived precursors had already returned to the normal range. Thus, MEG-CFC and GM-CFC in mouse bone marrow and spleen demonstrated significant differences in time, magnitude, and duration of response to CY, while the responses of these CFC were similar within specific organs. It is suggested that increased platelet counts in CY-treated mice may be attributable, at least in part, to alterations in feedback mechanisms which control megakaryocytopoiesis, thereby stimulating the megakaryocyte progenitor compartment. (35 Refs)

64. RESIDUAL INJURY TO THE HEMOPOIETIC MICROENVIRONMENT FOLLOWING SEQUENTIAL RADIATION AND ALKYLATING AGENTS.

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Diss Abstr Int [B]; 42(7):2730-B 1982

To assess the hemopoietic impact following combined modality therapy, mice received four weekly intraperitoneal doses of cyclophosphamide, 160 mg/kg (CY) one week after 1500 rad leg irradiation (LI). This treatment inhibited repopulation of endogenous nucleated cells to less than 60% of normal at 1, 2, 4, and 6 months postirradiation. Differential marrow counts revealed that 1500 rad LI + CY suppressed erythroblasts, myeloid, and lymphoid cells more than either modality alone. To directly assess the damage of sequential 1500 rad LI and CY on the microenvironment, marrow stromal cells were flushed from the femoral marrow and cultured as adherent cell colonies. They were suppressed to less than 30% normal for 3 months following combined modality treatment. Hemopoietic stem cells (CFU-S) and granulocyte-macrophage precursors (CFU-C) were supressed but exhibited different patterns of partial recovery. To determine whether busfulfan, an alkylating agent known to produce aplastic anemia, would cause microenvironmental damage similar to that seen following cyclophosphamide, mice received four weekly intraperitoneal doses of busulfan, 20 mg/kg (BU) one week after 1500 rad leg irradiation (LI). In general, the pattern of hemopoietic suppression following sequential radiation and busulfan was similar to that following sequential radiation and cyclophosphamide. However, at 4 and 6 months post-irradiation, the busulfan treated mice had a more severe suppression of CFU-S, CFU-C, and marrow stromal cells than mice treated with cyclophosphamide alone. In addition, an excessive number of myeloid blast cells and a severe erythroid depletion suggested that the BU-treated mice were preleukemic. (no Refs)

65. RESISTANCE OF RAT PERITONEAL MACROPHAGES TO HERPES SIMPLEX VIRUS. EFFECT OF TUMOR-BEARING RAT SERUM FACTOR(S) (MEETING ABSTRACT).

Bonina L, Iannello D, Merendino A, Arena A, Mastroeni P

Microbiology Institute, University of Messina, Messina, Italy

Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Macrophage restriction of virus replication has been shown to be closely related to virus strains or virus types and to the age of the infected host. In previous experiments we studied the ability of peritoneal rat macrophages to restrict HSV-2 replication in different experimental conditions. In particular we found that the replication of HSV-2 was significantly higher in macrophages obtained from tumor-bearing rats than in those obtained from normal adult animals. The depression of antiviral activity of macrophages was correlated with the development of neoplasia. In the present paper we describe the effect of tumor-bearing rat serum factor(s) on normal rat peritoneal macrophages activity against HSV-1 and HSV-2. The virus growth in macrophages was assessed by the 'infectious center assays', while single cycle growth curve of HSV-1 and HSV-2 was determined in macrophages in different experimental conditions. Normal rat peritoneal macrophages were preincubated with serum obtained from tumor-bearing rats at different times from tumor-graft, then assayed for restriction of HSV-1 and HSV-2 replication. Our results demonstrate a depression in normal macrophage activity against HSV-1 and HSV-2 induced by tumor-bearing rat serum factor(s). Differences in this inhibitory activity in relation to tumor development were found. (no Refs)

66. CHANGES IN NK ACTIVITY IN VIVO: EFFECTS ON THE GROWTH OF NK SENSITIVE AND NK RESISTANT TUMOR CELL VARIANTS (MEETING ABSTRACT).

Kawase I, Urdal DL, Brooks CG, Henney CS

Fred Hutchinson Cancer Research Center, Seattle, WA, 98104

Fed Proc; 41(3):475 1982

The growth of an NK sensitive variant (c127v-IC2) and of an NK resistant variant (c127av) of the L5178Y lymphoma was monitored in mice treated with agents which depressed or boosted NK activity. The difference in susceptibility of the variants to NK cells was reflected in their tumorigenicity. As few as one thousand c127av cells were tumorigenic whereas one million c127v-IC2 cells were required to generate tumors. NK cells bear asialo GM-1, but neither of the lymphoma cell variants showed chemically detectable amounts of this glycolipid. Intravenous injection of a rabbit anti-asialo GM-1 serum profoundly depressed splenic NK activity in CBA, DBA/2 and BALB/c nu/nu mice but had no effect on the development of cytotoxic T lymphocytes or cytotoxic macrophages. This treatment also led to a marked increase in tumorigenicity of c127v-IC2 cells in both syngeneic DBA/2 mice and in BALB/c nu/nu mice, but had no effect on the tumorigenicity of c127av cells. Intraperitoneal injection of poly I:C, which boosted NK activity, resulted in a significant retardation of the growth of c127v-IC2 cells, but not of c127av cells. The protection against c127v-IC2 growth afforded by poly I:C treatment was abrogated by iv injection of anti-asialo GM-1 serum. These results suggest that NK cells can play an important role in controlling tumor cell growth in vivo. (no Refs)

67. MECHANISMS OF CELLULAR CYTOTOXICITY MEDIATED BY EFFECTOR CELLS FROM RATS WITH SPONTANEOUS TUMORS.

Zoller M, Matzku S

Inst. Nuclear Medicine, German Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg 1, W. Germany

Int J Cancer; 30(2):181-185 1982

We have previously shown that effector cells from BD X rats bearing spontaneous tumors display increased cytotoxicity towards syngeneic tumor cells compared to effector cells from untreated rats. The increased in vitro cytotoxicity of lymphoid cells from tumor-bearing (TB) animals was not T-cell mediated and the question was raised, whether it was due solely to increased natural killer (NK) cell activity, or whether humoral factors could also be involved. We now prove that in a long-term assay, the presence of B cells is indeed mainly responsible for increased TB cytotoxicity, since: (1) after depletion of surface immunoglobulin positive cells (s-Ig+), TB cytotoxicity no longer exceeds cytotoxicity of effector cells from untreated rats; (2) mixtures of s-Ig+ cells from untreated rats restore the increased TB cytotoxicity; (3) addition of rabbit Fab' anti rat F(ab')2 reduces TB-effector cell cytotoxicity. A minor contribution of the increased TB cytotoxicity by activation/numerical increase of NK cells will be discussed. (Author abstract) (36 Refs)

68. NATURAL KILLER CELLS IN RESISTANCE TO VIRUS-INFECTED CELLS.

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Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, Bronx, NY, 10461

Springer Semin Immunopathol; 4(4):397-414 1982

The role of natural killer (NK) cells in resistance to virus-infected cells is reviewed. The following subject areas are covered: NK cells against virus-infected targets, induction of NK activity, characterization of NK cells, recognition of target cells, lytic mechanism, induction of resistance to target cells to interferon-induced NK lysis, the role of NK cells in vivo, and the relevance of NK cells to human disease. It is premature to evaluate the importance of NK cells in human cancer. (117 Refs)

69. CHARACTERIZATION OF THE NATURAL KILLER (NK) TARGET CELL POPULATION IN PRELEUKEMIC C57BL/6 MICE (MEETING ABSTRACT).

Munson D, Waksal SD, Parkinson DR

Departments of Medicine and Pathology, Tufts Cancer Research Center, Boston, MA, 02111

Fed Proc; 41(3):601 1982

Alterations in preleukemic cell populations were studied in the C57Bl/6 split-dose irradiation-induced model of thymic leukemia. We have previously shown NK cell activity to be depressed shortly after completion of the leukemogenic irradiation protocol. This is associated with the appearance of cells in the bone marrow and spleen of irradiated mice which are capable of blocking NK cell lysis of YAC-1 tumor targets. This blocking cell population is contained within the peanut agglutinin (PNA) positive cell fraction in both bone marrow and spleen. Studies using fluorescence activated cell sorter (FACS) have demonstrated cells expressing murine leukemia antigens (MuLV) in the bone marrow, spleen and thymus of irradiated mice at various time points following irradiation. During the same period, a large cell population is detectable initially in bone marrow and spleen and subsequently in thymus of irradiated mice. The present study characterizes the PNA positive, NK blocking cell population found in split-dose irradiated mice with respect to cell size, viral antigen expression and sensitivity to NK cell mediated cytolysis. (no Refs)

70. NATURAL CYTOTOXICITY OF ISOLATED RAT LIVER CELLS.

Cohen SA, Salazar D, Nolan JP

Dept. Medicine, Buffalo General Hosp., 100 High St., Buffalo, NY, 14203

J Immunol; 129(2):495-501 1982

Unfractionated live cells and parenchymal liver cells from untreated male Lewis rats were tested for natural cytotoxicity in a 4-hr 51chromium-release assay against YAC-1. Minimal cytotoxicity was observed. Nonparenchymal liver cells obtained by either differential centrifugation or metrizamide gradient centrifugation exerted strong cytotoxicity against YAC-1 and P815. Resident peritoneal exudate cells and spleen cells displayed cytotoxicity only against YAC-1. Furthermore, the cytotoxicity of these nonparenchymal liver cells was diminished by carbonyl iron treatment. Therefore, on the basis of these and other characteristics, the majority of the effector cells in the liver resemble tumoricidal macrophages. Finally, parenchymal liver cells or their cellfree supernatants were able to inhibit the cytotoxicity of these tumoricidal nonparenchymal liver cells, suggesting that the tumoricidal capacity of the liver was under some regulatory control. (Author abstract) (50 Refs)

71. NATURAL CYTOTOXICITY IN AKR/J MICE DURING ADJUVANT INDUCED AMYLOIDOGENESIS.

Fuhrman SA, Parkinson DR, Waksal SD, McAdam KP

(c/o Parkinson), Tufts Cancer Res. Center, 136 Harrison Ave., Boston, MA, 02111

Cell Immunol; 70(1):170-179 1982

The induction of amyloidosis in AKR mice has previously been shown to be associated with a decrease in the incidence of spontaneous thymic leukemia. Amyloid induction with azocasein depresses the activity of the natural killer (NK) cell, a cell believed to be important in the protection against the development of malignancy. In the present studies, therefore, we examined the response of the NK cell to the induction of amyloidosis in AKR mice. Rapid and long-term depression of NK cell activity against YAC-1 tumor cells was noted following intraperitoneal administration of complete Freund's adjuvant enriched with Mycobacterium butyricum. Mixing studies suggested that active suppression did not account for the observed decrease in NK cell activity. Although some NK cell activity was noted in ascitic fluid, redirection was not felt to account for the rapid and dramatic reduction in splenic NK cell activity. Furthermore, serum from adjuvant-treated but not control mice was found to significantly inhibit NK cell activity in vitro. These studies therefore suggested a role for a serum factor in the depression of this activity. The apparent paradox of decreased NK cell activity in a setting of diminished leukemogenesis is considered in relation to previous studies describing impaired T-cell functioning after the induction of amyloidosis. (Author abstract) (43 Refs)

72. INTERSPECIES TRANSFER OF TUMOR-SPECIFIC CELL-MEDIATED IMMUNITY FROM RABBITS TO HAMSTERS BY DIALYZABLE LEUKOCYTE EXTRACTS (MEETING ABSTRACT).

Tsang KY, Fudenberg HH, Gnagy MJ
Department of Basic and Clinical Immunology and Microbiology, Medical University of South Carolina, Charleston, SC, 29425
Med Pediatr Oncol; 10(1):103 1982

We have investigated the transfer of specific cell-mediated immunity (CMI) to tuberculin (PPD) and to osteosarcoma-associated antigens (OSAA) to hamsters with dialyzable leukocyte extracts (DLE) from immunized rabbits. The transfer of specific CMI was determined by leukocyte adherence inhibition (LAI) assay and skin testing. DLE was prepared from rabbits immunized with PPD or OSAA. Control DLE was prepared from rabbits injected with 0.85% NaCl. DLE was administered subcutaneously twice in 1 week to normal hamsters. Each injection contained DLE derived from 10(8) rabbit leukocytes. LAI assay and skin testing were performed 3 days after the injection of DLE. Ten ug and 20 ug of PPD or OSAA were used in LAI assays. Skin testing was performed by ear swelling assay. Tests were performed in the pinna of the ears of the hamsters by injecting 10 ug or 20 ug of PPD or OSAA diluted in 20 ul 0.85% NaCl. The ear thickness was measured with a microcaliper. Increases in ear thickness were calculated as the difference between the value measured before injection and at 4 hr and 24 hr after injection. In the LAI assay, using PPD or OSSA as antigen, significant inhibition was observed only with leukocytes from hamsters that had received PPD-specific or OSAA-specific rabbit DLE respectively. Similarly, significant ear swelling after injection of PPD or OSAA was observed only in hamsters that had received DLE from rabbits immunized with PPD or OSAA respectively. These results suggest that CMI specific for PPD or OSAA can be transferred to normal hamsters by DLE from immunized rabbits. (no Refs)

73. HISTOLOGICAL EFFECTS OF A COUPLED TUMOR PROTEIN ANTIGEN ON THE DEVELOPMENT OF TRANSPLANTED TUMORS IN C3H/HEJ MICE.

Phillip MJ, Molinari JA
Dept. Microbiology and Biochemistry, Univ. Detroit Sch. Dentistry, 2985 East Jefferson, Detroit, MI, 48207
Anticancer Res; 2(3):129-132 1982

Tumor proteins were extracted from spontaneous adenocarcinomas in C3H/HeJ mice, the proteins were coupled to human gamma globulin and the complex was used as a therapeutic device against transplanted C3H/HeJ mice. A comparison of the transplanted tumors on male and female animals showed no macroscopic or microscopic differences. A loss of cellular organization that was typically apparent when the neoplasm was passaged to recipient C3H/HeJ mice was observed. Treatment of tumor-infected mice with coupled tumor protein antigen (CTPA) presented a different microscopic picture. Infiltration by numerous mononuclear inflammatory cells into the tumor site suggested a development of a chronic immunopathological host response. Lymphocytes and macrophages were scattered throughout tissue specimens. Few, if any, plasma cells could be discerned in the tumor specimens. The observations appeared to be consistent with cell-mediated immune phenomena in vivo. While fragmented cellular debris scattered throughout the treated neoplastic tissues suggested that the macrophages were providing a direct anti-tumor effect, no direct cytotoxicity by either lymphocytes or macrophages could be discerned. Observations indicated that a degree of cell-mediated immunity was induced in animals treated with CTPA. (11 Refs)

74. SELECTIVE DOSE AND AGE DEPENDENT EFFECTS OF CIS-DICHLORODIAMMINE PLATINUM (CDDP) ON LYMPHOCYTE SUBPOPULATIONS IN MICE (MEETING ABSTRACT).

Bagasra O, Oosterhuis JW, Damjanov I
Department of Pathology, Hahnemann Medical College, Philadelphia, PA, 19102
Fed Proc; 41(3):934 1982

Cis-dichlorodiammine platinum (CDDP) is an effective anti-tumor agent in humans. Since the anti-tumor drugs generally have immunosuppressive effects, we have studied the immune responsiveness of BALB/c mice injected with 2 mg/kg or 12 mg/kg of CDDP. Young mice (8 wks of age) treated with 2 mg/kg CDDP mounted a primary splenic plaque forming cell response 2-2 1/2 times higher than normal controls to sheep erythrocytes (SRBC), a helper T-cell dependent (HTD) antigen and pneumococcal polysaccharide type III (SIII), a helper T-cell independent antigen (HTI). Young mice treated with 12 mg/kg of CDDP exhibited significant immunosuppression to both HTD and HTI antigens varying from 6 to 23% of control values. Adult mice (18 wks of age) injected with 2 mg/kg CDDP exhibited an enhanced PFC response to HTD and HTI antigens (182% and 336% of controls, respectively). Treatment of adult mice with 12 mg/kg of CDDP resulted in immunosuppression (61-78% of control). Immunoenhancement observed in low dose treatment animals was attributed to a selective loss of T-suppressor cells while immunosuppression was probably the result of injury to both T and B lymphocytes. (no Refs)

75. THE ANTIGENICITY OF ELECTROCAUTERIZED ALLOGENEIC TUMOR CELLS IN MICE.

Devereux DF, Sonis ST, Tilney NL, Collins JJ
Dept. Surgery, Peter Bent Brigham Hosp., 721 Huntington Ave., Boston, MA, 02115
J Surg Res; 33(1):17-22 1982

This study was conducted in order to establish the effects of electrocautery on the immunogenicity of allogeneic tumor cells as measured by cellular and humorally mediated responses. Balb/c mice were immunized with either cauterized or noncauterized EL4 tumor cells from C57Bl/6J mice. At 7 and 13 days postimmunization, humoral (CDC) and cell-mediated (CMC) responses were tested. Animals receiving cauterized or noncauterized EL4 cells had specific and significantly greater (p less than 0.001) CDC and CMC at 13 days than did nonimmunized animals. This study demonstrates that electrothermal destruction of allogeneic tumor cells does not prevent antigenic recognition by recipients. This might be clinically relevant if electrocoagulation is used to eradicate rectal and other carcinomas and yet allow immune recognition of tumor antigens should they exist. (Author abstract) (5 Refs)

76. REDUCTION OF BLADDER TUMOR GROWTH IN BCG TREATED MICE; ITS CORRELATION TO NATURAL KILLER CELL (NK) ACTIVITY AND INTERFERON LEVELS (MEETING ABSTRACT).

Shapiro A, Ratliff TL, Oakley DM, Catalona WJ
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., Boston, Massachussetts 254 pp., 1982.

We studied the effect of intravesical BCG treatment on the frequency of implantation and rate of growth of the transplantable N-[4-(5-nitro-2-furyl)]-2-thizolyl formide (FANFT)-induced bladder tumor, MBT-2. MBT-2 cells (10(6) cells/mouse in 0.1 ml) were instilled into the bladders of anesthetized C3H/HeJ female mice immediately after cauterizing the bladder for 5 seconds. Ninety-six hours later intravesical BCG treatment was initiated with a dose of 0.08 mg BCG/animal in 0.1 ml of water. Control animals were treated with diluent only. Treatment was continued at weekly intervals for 2-4 weeks and the following parameters were monitored: (1) tumor appearance, (2) weight of tumors, (3) NK (natural killer) activity, and (4) blood and urine interferon levels. BCG treatment resulted in a significant reduction in the appearance of tumors. Only 8/32 BCG-treated mice developed tumors while 23/31 appeared in controls. Furthermore, the tumors in the BCG-treated group were smaller tumors than those of control animals. The mechanism by which BCG treatment inhibits MBT-2 growth is unclear. Our results show significant elevation of NK activity in BCG-treated mice. Preliminary results suggest that NK modulation may be mediated by interferon although additional experiments are required to verify this observation. (no Refs)

77. THE ROLE OF INFLAMMATORY RESPONSE DURING THE EARLY PHASE OF TUMOR GROWTH (MEETING ABSTRACT).

Evans R

The Jackson Laboratory, Bar Harbor, ME

9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

This investigation was concerned with the relevance of the inflammatory response to early tumor growth and to what extent extravasation of circulating monocytes into the tumor site was a prerequisite for progressive tumor growth. C57BL/6J, C3H/HeJ and BALB/cBy mice were injected either im or sc with syngeneic tumor cells free of contaminating host leukocytes after treatment with a variety of anti-inflammatory reagents (hydrocortisone, indomethacin, azathioprine, reserpine) or after exposure to graded doses of whole body irradiation (WBI). The overall data indicated the tumor growth, estimated on the basis of the cellular composition of the tumor in conjunction with histological evaluation, was not necessarily inhibited immediately in treated mice. However, within 2-3 days after implantation of tumor cells, inhibition was apparent. Subsequent growth was impaired for a further 5-7 days, after which the cellularity of the tumor increased logarithmically. The monocyte and macrophage content of the tumors during the period of inhibition was variable and depended on the type or severity of treatment. For example, after indomethacin or low WBI the ratio of macrophages to other cell types was much the same as in control tumors, although absolute numbers of macrophages were much reduced. The ratio in hydrocortisone, azathioprine and heavily irradiated mice was significantly lower than that in control tumors, and reduced ratios were associated with depressed blood monocyte counts. Admixing peritoneal macrophages with tumor cells or bone marrow reconstitution prior to injection into mice resulted in enhanced tumor growth under anti-inflammatory conditions. The data indicate that a variety of factors may influence the inflammatory response, which appears to be a necessary component of early tumor growth. (no Refs)

EFFECTS OF ENDOGENOUS FACTORS AND APPLIED AGENTS ON CMI FUNCTION

78. ROLE OF INTERFERON IN NATURAL KILL OF HSV-1-INFECTED FIBROBLASTS.

Fitzgerald PA, Von Wussow P, Lopez C
Sloan-Kettering Inst. Cancer Res., 425 E. 68th St., New York, NY, 10021
J Immunol; 129(2):819-823 1982

The production of interferon during natural killer (NK) assays against HSV-1-infected fibroblasts (NK(HSV-1)) was studied to determine whether this interferon was responsible for inducing the preferential lysis of herpes-virus-infected target cells over uninfected target cells. The interferon produced during NK(HSV-1) assays was analyzed and found to have the properties of HU-IFN-alpha. Little or no IFN was produced during NK assays against uninfected fibroblasts (NK(FS)) or K562 (NK(K562)) cells. Although the appearance of interferon in the culture supernatants seemed to parallel the development of cytotoxicity during NK(HSV-1) assays, the levels of cytotoxicity and IFN generated did not correlate, arguing against a strict quantitative dependence of cytotoxicity upon IFN production. NK(K562) and NK(FS) cytotoxicity developed with little or no production of IFN. When IFN-pretreated effector cells were used, there was still a preferential lysis of infected over uninfected target cells. This preferential lysis by IFN-treated effector cells of infected over uninfected targets was seen as early as 2 hr into the assay. Anti-IFN antibodies added to the NK assays, although neutralizing all the IFN produced during the assays, had no effect on NK(FS) or NK(K562) cytotoxic activity and caused a slight reduction of NK(HSV-1) activity only in one of three experiments. We conclude that although IFN is generated during NK(HSV-1) assays, this IFN cannot solely account for the increased lysis of infected over uninfected cells and that NK(HSV-1) activity is in some other way dependent on the virus infection. (Author abstract) (34 Refs)

79. THE ROLE OF INTERFERON IN THE MAINTENANCE OF NATURAL KILLING BY HUMAN T LYMPHOCYTE SUBSETS (MEETING ABSTRACT).

Peterman GM, Klimpel GR, Stanton GJ, Altman LC
University of Washington, Seattle, WA, 98195
Fed Proc; 41(3):801 1982

We have previously reported that freshly isolated human T lymphocyte subsets differ in their ability to kill K562 tumor cells in assays of natural killing and that these cells maintain their cytolytic capacity when stimulated in mixed lymphocyte culture (MLC). In order to assess the role of interferon (IFN) in K562 cytolysis, we examined IFN levels in supernatants from MLC stimulated T cell subsets and the role of exogenous IFN in the maintenance of K562 killing. IFN levels were measured by viral plaque reduction. T cells were isolated by srbc rosette formation and Ficoll-Hypaque centrifugation. T cells which lost the ability to form srbc rosettes after incubation in 5mM theophylline (T-sens cells) and T cells which retained this ability (T-res cells) produced equivalent levels of IFN when stimulated in MLC. The IFN produced by these T cell populations was completely neutralized by antisera against IFN gamma while antibodies directed against IFN alpha and IFN beta had no effect. In contrast, T cells cultured alone failed to produce IFN and did not kill K562. Addition of partially purified IFN gamma (10(5) U/mg protein) to cultured T cell subsets markedly enhanced their ability to kill K562. These results suggest that maintenance of K562 cytolysis by MLC stimulated T cells is mediated by the production of IFN gamma. (no Refs)

80. IN VITRO STUDY OF THE EFFECTS OF HUMAN LEUKOCYTE INTERFERON ON CELL DIVISION AND NATURAL KILLER CELL ACTIVITY.

Gorog G, Onody K, Toth M, Benczur M, Petranyi Gy, Beladi I, Hollan Zs
EGYT Gyogyszervegyeszeti Gyar, Budapest, Hungary
Orv Hetil; 123(24):1479-1482 1982

The in vitro study of the effects of different interferon preparations demonstrated considerable interindividual and interpreparation differences in the inhibition of mitogen-induced blast transformation of human peripheral lymphocytes and in the enhancement of the natural killer cell activity. The effects were, however, consistently dose-dependent when tested in several individuals. Positive correlation was found between the interferon-induced inhibition of thymidine uptake by tumor cell lines (Raji, Daudi, K-562) and the antiviral effect, which suggests the potential value of this method for the measurement of the interferon activity. (26 Refs) (In HUN)

81. INHIBITION OF TRANSPLANTED HUMAN OSTEOSARCOMA (HOS) TUMORS IN ATHYMIC MICE BY HUMAN INTERFERON (HUIFN) (MEETING ABSTRACT).

Glasgow LA, Kosak KM, Kelsey DK
Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT
Pediatr Res; 16(4,part2):205A 1982

HuIFN is being evaluated as a potential therapeutic agent for human malignancies. Unfortunately clinical trials are being initiated with minimal background data from preliminary studies in animal models. We developed an experimental model utilizing the sc transplantation of HOS cells into athymic mice. Prior to treatment in vivo, the growth of HOS cells in culture were shown to be inhibited by lymphoblastoid HuIFN. In contrast a human melanoma cell line was resistant to the antiproliferative effect of HuIFN. In athymic mice HuIFN administered sc for 7d completely prevented or inhibited the growth of HOS tumors. The in vitro resistance of the melanoma cells was also reflected in vivo. The mechanism thru which HuIFN exerts its antitumor activity in vivo remains only partially defined. Because of the species specificity of IFN, we postulated that HuIFN would only express antiproliferative activity in the mouse. This was confirmed by the demonstration that in vitro HuIFN augmented human (21% specific 51Cr release to 75%), but not murine NK (natural killer) cell activity; activated human monocytes to be cytotoxic for HOS cells, but failed to activate murine macrophages. (no Refs)

82. FIBRONECTIN ENHANCES IN VITRO MONOCYTE-MACROPHAGE-MEDIATED TUMORICIDAL ACTIVITY.

Perri RT, Kay NE, McCarthy J, Vessella RL, Jacob HS, Furcht LT
Hematology-Oncology Section (IIIE), Veterans Admin. Medical Center, 54th St. and 48th Ave. South, Minneapolis, MN, 55417
Blood; 60(2):430-435 1982

Control of neoplastic proliferation reflects in part monocyte/macrophage destruction of target cells - destruction that evidently requires cell-cell interaction. We herein show it to involve the natural plasma opsonin, fibronectin. With two cultured human tumor lines - Malme melanoma and CAK-I renal carcinoma cells - addition of fibronectin, purified to homogeneity, enhances macrophage-mediated cytotoxicity two to four fold (p less than 0.01). Both fresh human monocytes or the U-937-cultured macrophage line become more lethal to tumor cells with added fibronectin. The fibronectin-enhanced monocyte and U-937 tumoricidal activity occurred in a dose-dependent fashion. Specificity of fibronectin's action was validated by use of affinity-purified rabbit antifibronectin antibody, which completely abated its enhancement of tumoricidal activity. Enhancement of tumoricidal activity did not occur when monocytes or U-937 were exposed to fibronectin-coated plates. However, the addition of soluble fibronectin to fibronectin-coated plates was then capable of enhancing cytocidal activity. These studies demonstrate that human fibronectin is capable of increasing both fresh and cultured human monocyte tumor-directed cytotoxicity. Fibronectin appears to be a potentially important circulating molecule that may favorably influence human monocyte tumor cell cytotoxicity. (Author abstract) (36 Refs)

83. MACROPHAGE REGULATION OF NATURAL KILLER CELL ACTIVITY IN AGED RATS (MEETING ABSTRACT).

Bash JA, Robinson E, Vogel D
Immunologic Oncology Division, Lombardi Cancer Center, Georgetown University, Washington, DC, 20007
Fed Proc; 41(3):475 1982

Natural killer (NK) activity is markedly deficient in aged rats concomitant with an increased incidence of spontaneous tumors. The present study was initiated to determine if a regulatory mechanism mediated by macrophages could account for this age-related depression. Fischer 344 rats of ages 4-6 weeks (young) and 24-30 months (old) were compared for NK activity against 51Cr-labelled YAC-1 mouse lymphoma cells in a standard 4 hr assay. Old rat splenic NK activity at an 100:1 effector:target ratio was less than 10% specific release while young rat activity at the same ratio was about 75%. Removal of adherent cells on G-10 Sephadex resulted in a greater than 10-fold enhancement of NK activity of old spleen cells while young spleen cells NK was unaffected or slightly reduced. Rat fibroblast interferon (IFN) boosted old rat NK activity 3-5 fold but only slightly enhanced the already high young NK activity. Prostaglandin E2 (PGE2) at 10-6M however totally abolished NK activity in old rats even with concomitant IFN treatment. PGE2 reduced young NK activity to a much lesser extent. These results suggest that old rat NK cells are much more sensitive to the inhibitory effect of PGE2 than are young NK cells and that macrophages as producers of PGE2 may become important suppressors of NK activity with advancing age. (no Refs)

84. TUMORICIDAL EFFECT OF MACROPHAGES EXPOSED TO ADRIAMYCIN IN VIVO OR IN VITRO.

Martin F, Caignard A, Olsson O, Jeannin JF, Leclerc A
Res. Group Digestive Tumors, Lab. Immunology, Institut National de la Sante et de la Recherche Medicale, 21033 Dijon, France
Cancer Res; 42(9):3851-3857 1982

Peritoneal macrophages from BD IX rats collected 24 hr after an ip injection of Adriamycin (10 mg/kg) were cytotoxic to syngeneic cancer cells in culture. In contrast, incubation in vitro in Adriamycin solutions did not evoke tumoricidal activity in peritoneal macrophages, whatever the incubation time (from 1 to 24 hr) and the Adriamycin concentration (from 1 ng to 100 ug/ml). Macrophages incubated with Adriamycin in vitro accumulated the drug in their nuclei, whereas macrophages from animals receiving Adriamycin in vivo accumulated it in cytoplasmic vacuoles. Early observation of peritoneal cells after in vivo exposure to Adriamycin shows that Adriamycin is concentrated in mast cell granules which are released and then phagocytosed by peritoneal macrophages. Mast cells exposed to Adriamycin in vitro can induced macrophages to become cytotoxic. These facts explain the difference between macrophages exposed to Adriamycin in vivo and in vitro. Adriamycin fluorescence appears in nuclei of cancer cells incubated with in vivo-labeled macrophages, suggesting that macrophages can directly transfer the drug into cancer cells and therefore play a role in the Adriamycin antitumor effect. (Author abstract) (22 Refs)

85. IGG2A MONOCLONAL ANTIBODIES INHIBIT HUMAN TUMOR GROWTH THROUGH INTERACTION WITH EFFECTOR CELLS.

Herlyn D, Koprowski H
Wistar Inst. Anatomy and Biology, 36th and Spruce St., Philadelphia, PA, 19104
Proc Natl Acad Sci USA; 79(15):4761-4765 1982

Monoclonal antibodies of IgG2 isotype specifically inhibited growth of human tumors in nude mice. Twenty-three monoclonal antibodies of other isotypes showed no tumoricidal reactivity. Complement depletion of nude mice had no effect on tumor suppression by monoclonal antibody. The role of T and killer cells as mediators of the monoclonal antibody effect in nude mice was virtually excluded. On the other hand, macrophages were strongly incriminated as effector cells because silica treatment of nude mice abolished the tumoricidal effect of monoclonal antibody. IgG2a monoclonal antibody-dependent macrophage-mediated cytotoxicity assays with human tumor cells in culture resulted in specific lysis of tumor cells. (Author abstract) (26 Refs)

86. EVIDENCE FOR TUMOR ASSOCIATED FETAL ANTIGEN BINDING TO HUMAN NATURAL KILLER CELLS (MEETING ABSTRACT).

Hogan KT, Harris DT, Evans DL
Bowman Gray School of Medicine, Winston-Salem, NC, 27012
Fed Proc; 41(3):818 1982

TAFA-II, a tumor associated fetal antigen, isolated from methylcholanthrene fibrosarcomas in NBR rats, is biochemically similar to interleukin-1 (IL-1). These peptides have similar molecular weights, pI and amino acid composition. Both modulate cytotoxic T cell activity and induce granulocytosis in the rat. TAFA-II however, has been shown to suppress NK cell activity in humans, rats and mice. The possibility exists that TAFA-II may be an altered form of IL-1, or a member of a related family of peptides which are expressed by tumor cells. We have determined the optimal conditions for TAFA-II binding by human peripheral blood leukocytes (PBL). Binding is greatest at pH 9-11 (4C). Binding is rapid and equilibrium is achieved within 10 minutes. Some individuals demonstrate saturable binding at approximately 10(-13) moles/10(6) PBL. 125I or fluorescein (FITC) labeled TAFA-II was used to identify the cell population which binds TAFA. PBL were pulse labeled with 125I-TAFA-II or FITC-TAFA-II and separated on 40-55% discontinuous Percoll density gradients. Fractions producing the greatest enrichment for NK cell cytotoxicity (K562 targets) had large granular lymphocyte morphology. These same fractions also contained cells (NK and lymphocytes) which bound labeled TAFA-II. These data indicate that TAFA-II binds NK cells, and as such represents a possible mechanism of regulation of immunosurveillance. (no Refs)

87. IN VIVO AND IN VITRO MODULATION BY BIOLOGICAL RESPONSE MODIFIERS OF HUMAN NK CELL ACTIVITY (MEETING ABSTRACT).

Rey A, Caplaol D, Favier F, Rucheton M, Esteve C, Serrou B
Department of Chemo-Immunotherapy, Centre Paul Lamarque, Montpellier, France
Fed Proc; 41(3):804 1982

Human ARFC (autologous rosette forming cells) have been described at length by our group. Purification of peripheral blood lymphocytes capable of forming autologous rosettes can be performed with satisfactory yield and enrichment by centrifugation on a percoll cushion. Purified ARFC express HTLA, possess Fc receptor for IgM but not for IgG and are OKT4 positive. ARFC support only weak ADCC (antibody dependent cellular cytotoxicity) and NK (natural killer) activity but are responsible for autologous and allogeneic MLC (mixed leukocyte culture), responding strongly to phytohemagglutinin and weakly to pokeweed mitogen and Con A (concanavalin A). They demonstrate no suppressor activity after Con A stimulation and are JRA negative. Cytochemical and electron microscopic characterization suggest that ARFC form a homogenous cell subset. A clinical study including 50 malignant melanoma patients and 50 breast cancer patients was undertaken to evaluate the prognostic value of ARFC. The results show that 20% or less ARFC in peripheral blood samples represents an evolutive status. Variation of ARFC levels in malignant melanoma patients paralleled variations in beta-2-microglobulin. Simultaneous increase of both parameters correlated with clinical aggravation in 90% of cases. ARFC below 20% in breast cancer patients preceded advancing metastatic disease in 42% of cases. (no Refs)

88. THE INHIBITORY ROLE OF THE CARCINOEMBRYONIC ANTIGEN IN THE BLAST TRANSFORMATION OF THE NORMAL HUMAN LYMPHOCYTES (MEETING ABSTRACT).

Kotnik V, Krivec V, Vozelju M, Herzog B
Institute of Microbiology, Ljubljana, Yugoslavia
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey, Turkish Society of Immunology 354 pp., 1982.

The Inhibitory Role of the Carcinoembronic antigen (CEA) in concentrations from 20 ug, and 5 ug per milliliter reduced in vitro the blast transformation of the normal human lymphocytes. The same phenomenon was observed also in blood samples from the patients suffering from the CEA producing carcinomas. The method used to study the CEA effect on the lymphocytes was modification of the blast transformation test convenient for antigen testing assays. The observed suppression was dose and time dependent and comprised reduction of the blast transformation from 17.7% to 74% of the 2H-thymidine incorporation to the appropriate control respectively. The suppression was observed in assays with sensibilized and unsensibilized human lymphocytes. The suppression was unspecific and mechanism supposed could be the result of the suppressor cell function or direct inhibition through a CEA receptor. (no Refs)

89. T HELPER CELLS IN IMMUNE MICE AMPLIFY THE PRIMARY ANTITUMOR CYTOTOXIC RESPONSE.

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J Immunol; 129(2):856-859 1982

In this report we examine the influence of splenic helper cells in the primary cytotoxic T lymphocyte (CTL) response against syngeneic murine leukemia virus-(MuLV) induced tumor cells. We identify an Lyt-1+ 800 R radiation-resistant helper T cell that will amplify the in vitro generation of CTL against syngeneic tumor cells from nonimmune spleen cells. (Author abstract) (25 Refs)

90. IMMUNOGENICITY CHANGES INVERSELY WITH IMMUNOSENSITIVITY DURING IN VITRO DIFFERENTIATION OF HUMAN TERATOCARCINOMA (MEETING ABSTRACT).

Dewolf WC, Carroll PG
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association Missouri. American Urological Association 254 pp., 1982.

The in vitro teratocarcinoma (TC) model provides a unique setting for analysis of developmental regulation in terms of embryonic and malignant gene expression; this is true because, in contrast to other kinds of tumors, it has the potential to differentiate into tissues derived from all three primary germ layers. In this study, the effects of in vitro differentiation were measured in terms of two fundamental cellular immune properties of tumor cells ie immunogenicity and immunosensitivity. Four characterized human TC cell lines were used. In vitro differentiation was induced by cell culture in the presence of retinoic acid with or without cAMP. TC immunogiuecity was measured by mixed tumor-lymphocyte assay. Results are expressed as mean triplicate values of incorporated 3HTdR (thymidine) by autologous or allogeneic responder lymphocytes. Immunosensitivity was assayed by release of 51Cr from TC target cells upon lysis by activated NK (natural killer) cells; likewise target specificities were checked by cold target inhibition. All 51Cr release assays were performed at multiple E:T ratios. The results showed 1) immunogenicity increased with differentiation and was not associated with HLA-DR expression, 2) immunosensitivity decreased with differentiation, 3) the TC CML target specificity is on all TC cells but not on lymphocytes or lymphoblastoid cells. This work supports the overall concept that the natural killing mechanism functions as a primitive immune system to form a cell mediated resistance barrier against the outgrowth of certain undifferentiated tumor cells. (no Refs)

91. DEVELOPMENT OF LONG-TERM CELL LINES AND LYMPHOID CLONES REACTIVE AGAINST MURINE AND HUMAN TUMORS: A NEW APPROACH TO THE ADOPTIVE IMMUNOTHERAPY OF CANCER.

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Surgery; 92(2):328-336 1982

We have investigated the use of T-cell growth factor (TCGF) to isolate and grow, in long-term culture, lymphoid cells with immunologic reactivity directed against syngeneic murine and autologous human tumors. Splenocytes from mice immune to a methylcholanthrene-induced sarcoma were expanded in TCGF, both before and after in vitro mixed lymphocyte-tumor cultures, and expressed high levels of cytotoxicity for fresh syngeneic solid tumor cells. Cloned lines have been isolated with a high level of specific lysis for the immunizing tumor. Similar studies of cytotoxic reactivity to a syngeneic FBL-3 lymphoma have given rise to long-term cytotoxic cell lines growing in TCGF capable of curing mice with disseminated lymphoma in adoptive transfer studies. Exposure to

TCGF, of human peripheral lymphoid cells from cancer-bearing patients, results in the development of cytotoxicity to autologous fresh tumor. We have used clonal analysis by limiting dilution techniques to isolate individual cloned cells with this autologous antitumor reactivity. Infusion of autologous cytotoxic cells expanded 10,000-fold in TCGF and labeled with 111In into three cancer patients resulted in cell localization initially to the lung and subsequently to the liver and spleen. The application of these techniques for the cloning and expansion of antitumor T-lymphoid cells in TCGF has offered a new approach to adoptive immunotherapy. (Author abstract) (18 Refs)

92. EFFECT OF ACYCLOVIR ON VARIOUS MURINE IN VIVO AND IN VITRO IMMUNOLOGIC ASSAY SYSTEMS.

Quinn RP, Wolberg G, Medzihradsky J, Elion GB
Wellcome Res. Lab., 3030 Cornwallis Road, Research Triangle Park, NC, 27709
Am J Med; 73(1A):62-66 1982

In two in vitro tests, lymphocyte-mediated cytotoxicity and neutrophil chemotaxis, acyclovir showed no inhibitory effects at concentrations as high as 600 uM. The compound inhibited rosette formation with nonimmune mouse lymphocytes in vitro by approximately 50% at 15.8 uM. The significance of this inhibition is unclear. In four in vivo tests in mice which measured humoral and cell-mediated immunity (complement-dependent cellular cytotoxicity, complement-independent cellular cytotoxicity, delayed hypersensitivity and graft vs host reaction) acyclovir showed no inhibitory effects at single doses up to 200 mg/kg given on Day 2 after antigenic stimulation. Four daily doses of acyclovir at 50 mg/kg per day had no effect on the numbers of hemolytic IgM antibody-forming cells in the spleen when assayed on Day 4. At the higher dosage of 100 mg/kg per day for 4 days, there was a slight reduction in the numbers of these cells. There was no significant decrease in hemagglutinin or hemolysin antibody titers after four daily doses of acyclovir up to 200 mg/kg. (Author abstract) (16 Refs)

93. INHIBITION OF CONCANAVALIN A RESPONSE DURING OSTEOPETROSIS VIRUS INFECTION.

Price JA, Smith RE
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Cancer Res; 42(9):3617-3624 1982

Infection of animals with oncogenic viruses frequently leads to an immunosuppressed state. We have examined immunosuppression induced by an avian osteopetrosis virus, myeloblastosis-associated virus of subgroup B inducing osteopetrosis [MAV-2(O)], and our results suggest that this virus induces immunosuppression by a novel mechanism. Lymphoid cells from osteopetrotic chickens did not respond to a wide dose range of concanavalin A (Con A) over a wide cell density range. Failure to undergo blastogenesis was not due to a lack of Con A-binding sites, since 125I-labeled Con A bound to lymphocytes from infected and uninfected chickens. Infected lymphocytes failed to respond to uninfected chickens. Infected lymphocytes failed to respond to sodium metaperiodate stimulation, indicating that failure of blastogenesis was not due to a blockage of Con A receptor sites. MAV-2(O) infection of chicks 8 days of age resulted in a transient immunosuppression which appeared 1 to 2 wk after infection. Cell-mixing experiments showed that MAV-2(O)-induced immunosuppression was not attributable to suppressor cells. In contrast, adherent cells from normal lymphoid preparations restored mitogenicity to lymphocytes from MAV-2(O)-infected animals. Adherent cells were present in the spleen and peripheral blood lymphocytes of MAV-2(O)-infected chickens in numbers comparable to those of the uninfected animal, and both sets of cells contained Fc-dependent phagocytic activity and nonspecific esterase. Peritoneal exudate cells were elicited from osteopetrotic and normal chickens in similar numbers. We conclude that MAV-2(O) induces immunosuppression by interfering with an accessory function of macrophage-like adherent cells. (Author abstract) (55 Refs)

94. THE DIFFERENTIAL SENSITIVITY OF T CELL IMMUNE FUNCTIONS TO VINCRISTINE AND VINBLASTINE.

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Int J Immunopharmacol; 4(3):187-193 1982

The effects of vincristine (VCR) and vinblastine (VBL) on various parameters of murine immune function were investigated. The precursors of non-specific culture-induced suppressor cells were more sensitive to VLB than to VCR when the drugs were injected at equally toxic doses into spleen donor mice or when they were added at equimolar concentration to the suppressor generation cultures. Addition of arabinofuranosylcytosine to the suppressor generation culture inhibited the development of suppressor activity, indicating that cell proliferation is a necessary component during differentiation of suppressor cell precursors into mature cells. Adriamycin did not abolish the development of suppressor activity when added to suppressor generation cultures. When VLB was injected into mice, the cytotoxic T lymphocyte responses developed by spleen cells in culture against alloantigens were lower than those of controls even though under the same conditions VLB abolished or prevented the development of suppressor functions. T Cell responses were more sensitive to VLB than to VCR, while B cell responses were more sensitive to VCR. (34 Refs)

95. EFFECT OF IN VITRO CYCLOSPORIN A (CYA) THREATMENT ON HUMAN NATURAL AND ANTIBODY-DEPENDENT CELL MEDIATED CYTOTOXICITY (MEETING ABSTRACT).

Lang I, Shao-hsien C, Gunn H, Lydyard P
Department of Immunology, Middlesex Hospital Medical School, London, England
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Since both ADCC (antibody dependent cell cytotoxicity) and NK (natural killer) cell activity may play a role in the immunological defense against malignancies, and CyA as a potent immunosuppressive agent might also affect the anti-tumor defense mechanisms of the treated subjects, we have studied the in vitro effect of CyA on human ADCC and NK activities. Concentrations of 0.1-10.0 ug/ml CyA do not directly inhibit the lysis of 51-Cr labelled K562 target cells by human peripheral blood NK cells nor of antibody-coated chicken red blood cells by ADCC effector cells. Pretreatment of effector cells with CyA for 18 hr still failed to affect NK or ADCC effector function. However, induction of NK cell activity by overnight pretreatment of effector cells by PolyIC is inhibited by as little as 1 ug/ml CyA. The mechanism of inhibition may involve a direct effect of CyA on 'induced' or 'activated' NK cells or inhibition of the release of PolyIC induced interferon from lymphocytes. (no Refs)

96. ENHANCING ACTIVITY OF VARIOUS IMMUNOAUGMENTING AGENTS ON THE DELAYED-TYPE HYPERSENSITIVITY RESPONSE IN MICE.

Bartocci A, Read EL, Welker RD, Schlick E, Papademetriou V, Chirigos MA
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Cancer Res; 42(9):3514-3518 1982

Six immunoaugmenting agents were tested in the delayed-type hypersensitivity reaction (DTH) in normal BALB/c x DBA/2 mice. The agents tested, levan, lentinan, mannozym, maleic anhydride divinyl ether, polyriboinosinic-polycytidylic acid-poly-L-lysine, and highly purified L-cell interferon, gave significant increases in the DTH response above the sheep red blood cell control. The schedule of doses for each agent corresponded with previous experiments from this laboratory of the maximum natural killer cell activity, macrophage activation, and interferon induction. Highly purified L-cell interferon was capable of eliciting a significant DTH response when given 4 hr after the initial challenge with sheep erythrocytes. In addition, lambda-carrageenan, a macrophage-cytotoxic agent which can render the macrophage inactive, was found to suppress the DTH response to levels slightly above phosphate-buffered saline controls. The carrageenan-induced suppression of the DTH response could be abrogated by coadministration with immunoaugmenting agents to levels attained with the immunoaugmenting agents alone. (Author abstract) (32 Refs)

97. ANTITUMOR ACTIVITY AND HYDROGEN PEROXIDE RELEASE BY MACROPHAGES ELICITED BY TREHALOSE DIESTERS.

Lepoivre M, Tenu JP, Lemaire G, Petit JF
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J Immunol; 129(2):860-866 1982

Trehalose diesters (natural 6,6'-trehalose dimycolate from Mycobacterium tuberculosis or synthetic (a 76 carbon atom analogue)), when suspended in water, given stable and well-defined emulsions. These emulsions, injected ip in mice significantly limit the growth of P815 syngeneic mastocytoma cells. They elicit macrophages with a cytostatic activity against P815 cells in vitro, strong enough to be expressed at low effector to target ratios (E/T = 1.4) or after a short coincubation period (2 hr). The antitumor potential of these macrophages seems to coincide with their ability to release H2O2 upon pharmacologic triggering. Depressed levels of alkaline phosphodiesterase and beta-galactosidase are proposed as other biochemical markers of cytostatic macrophages. (Author abstract) (44 Refs)

98. THE EFFECTS OF DIET AND CARCINOGEN ON THE NATURAL KILLER CELL ACTIVITY OF SPRAGUE DAWLEY RATS.

Longley RE
The University of Oklahoma, Norman, OK
Diss Abstr Int [B]; 42(11):4355-B 1982

This study was conducted to determine if dietary fat and/or administration of 7,12 dimethylbenz(a)anthracene (DMBA) to Sprague Dawley rats affected the natural killer (NK) cell activity of these animals. The inhibitory activity of NK cells was dependent on the quantity of fat in the diet of the rats from which these cells were obtained. Rats which were fed a 20% corn oil diet (high fat) generally had lower levels of inhibitory activity against YAC-1 tumor cells compared to rats fed a diet containing 2% linoleic acid (low fat). While choline deficiency or treatment with DMBA did not alter NK cell activity in either dietary group, the combination of both factors caused a significant reduction in NK cell activity when rats were maintained on a high fat diet. The proliferative activity of NK cells were generally higher in rats on the high fat diet compared to rats on the low fat diet. NK-induced inhibition of YAC-1 cell proliferation correlated inversely with the proliferative activity of the NK cells. Some of the rats fed high fat diets had NK cells whose proliferative activity was approximately twice that of rats fed low fat diets, and whose corresponding inhibitory activity against YAC-1 tumor cells was one-half that of rats on low fat diets. NK cell activity was not constant during the period of study, but tended to display cyclic responses, particularly in rats in the high fat diet. There was no difference in the level of inhibitory activity of NK cells from rats on a low fat diet compared to rats on the high fat diet, when the R2T2 tumor cell line was used as the target cell. While the ability of NK cells to inhibit proliferation of YAC-1 tumor cells in vitro was diet dependent, the inability to show diet dependency on the ability of NK cells to inhibit the proliferation of R2T2 tumor cells in vitro did not necessarily rule out an in vivo role for NK cells in the resistance of rats to DMBA-induced tumors. (no Refs)

99. CIMETIDINE AS IMMUNOREGULATOR (MEETING ABSTRACT).

Strejcek J, Suhajova E, Jira M, Fisa M

Faculty of Medicine and Hygiene, Charles University, Prague, Czechoslovakia

Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Cimetidine significantly prolonged survival of tumor-inoculated mice and increased the blastic transformation of lymphocytes after non-specific stimulation with phytohemagglutinins. It seems that cimetidine has an inhibitory action on supressor T-lymphocytes. (no Refs)

100. THE IN VITRO EFFECT OF BENZO-PYRENE ON THE IMMUNE RESPONSE (MEETING ABSTRACT).

Rossi RM, Urso P, Gengozian N

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Fed Proc; 41(3):446 1982

The potent carcinogen, benzo(a)pyrene (BP), was shown to decrease the in vitro ability of mouse (C3H) spleen cells to respond to a foreign antigen, (sheep red blood cells (SRBC)). At concentrations as low as 10(-8) molar, BP inhibited the antigen-antibody response as measured by a reduction in the plaque forming cells (PFC) determined by using a modified Jerne plaque technique. The maximal inhibition was obtained at 4 x 10(-4) molar, (100%), with a gradual reduction occurring in the range of 10(-8) to 10(-5) molar. Lower concentrations resulted in no inhibition or a slight enhancement of the PFC response. The noncarcinogenic analog of benzo(a)pyrene, benzo(e)pyrene (B(e)P), produced no inhibition between 10(-5) and 10(-7) molar. Further, 10(-5) and 10(-6) M BP severely depressed the mixed lymphocyte response of normal spleen cells. A single dose of BP, (150 ug/g body weight), during gestation, resulted in a severe depression of the anti-SRBC PFC response that persisted throughout life. These results indicate that exposure of immunocompetent (T and B) cells to small doses of BP disrupt events leading to humoral and cell mediated immune responses. (no Refs)

101. SUPPRESSION OF THE CYTOTOXIC RESPONSE OF MOUSE LYMPHOCYTES TO SYNGENEIC TUMOR CELLS BY TUMOR-PROMOTING PHORBOL ESTER.

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Cancer Res; 42(9):3601-3606 1982

We have investigated the effects of tumor-promoting phorbol esters on the generation of T-killer cells against syngeneic tumor cells in tissue culture. C57BL/6 or BALB/c spleen cells were cultured with irradiated EL-4 or MPC-11 tumor cells, respectively, for 3 to 7 days at responder:stimulator ratios of 25:1 to 200:1. Lysis was measured in a 4-hr 51Cr release assay. During the sensitization phase, 12-O-tetradecanoylphorbol-13-acetate (TPA) at concentrations as low as 10 ng/ml inhibited the response by 90 to 100% at all responder:stimulator ratios and when added on Day 0, 1, 2, or 4 of a 5-day assay. Thus, TPA was able to suppress the response following successful activation of lymphocytes, since cytotoxicity could be detected as early as Day 3. Addition of TPA on Day 0 caused complete suppression of lysis when measured on Day 3, 5, or 7, indicating that the suppression was not due to a change in the kinetics of the cytotoxic response. The degree of suppression caused by five different phorbol compounds was positively correlated with their tumor-promoting activity. TPA was much less suppressive when added at the effector phase. Indomethacin, an inhibitor of prostaglandin synthesis, did not reverse the TPA effect even when added daily, beginning 3 days before the addition of TPA. The data suggest that one mechanism of phorbol ester tumor promotion may be the inhibition of T-cell immunity against tumor cells initiated by carcinogens. (Author abstract) (42 Refs)

102. INDOMETHACIN SENSITIVE SUPPRESSOR CELL ACTIVITY IN HEAD AND NECK CANCER PATIENTS PRE- AND POSTIRRADIATION THERAPY.

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Cancer; 50(3):483-489 1982

The effects of the addition of indomethacin to PHA or Con A stimulated lymphocytes from patients with untreated squamous cell carcinoma of the head and neck or from patients with the disease who have just finished irradiation therapy from the disease was quantitated and compared to those of the control group. Lymphocytes from 8 of 26 patients with untreated carcinoma were significantly augmented by the addition of indomethacin. The remaining 18 patients were equal to the controls. For all 17 patients who had just finished extensive field irradiation therapy, significant enhancement of PHA and Con A reactivity by indomethacin was found, which did not appear to be solely a function of low baseline mitogen reactivity. In additional studies, stimulated lymphocytes of irradiated patients were tested for their sensitivity to the inhibitory effect of PGE2. The mitogen treated lymphocytes from all patients that had just finished irradiation therapy were found to be significantly more sensitive to the inhibition by PGE2 as compared to the normal lymphocyte response. This effect was also found not to be related merely to a low PHA or Con A reactivity of the lymphocytes. In both patient groups there was a striking correlation between the percent augmentation of indomethacin and the percent inhibition of PGE2 in that when the percent augmentation values were low so were percent inhibition values and when the degree of augmentation by indomethacin was elevated so was the inhibition by PGE2. This data suggests that increase sensitivity of stimulated lymphocytes to PGE2 may be responsible, at least in part, for the depressed mitogen response and the significant augmentation of this immune response by indomethacin in about 1/3 of the untreated patients with advanced head and neck carcinoma and in those patients who have just finished irradiation therapy. The results of this study support the hypothesis that perhaps patients receiving irradiation therapy may benefit by the oral administration of indomethacin, an approach that needs further consideration. (Author abstract) (33 Refs)

103. EFFECTS OF DIPHENYLHYDANTOIN ON KILLER CELL ACTIVITY AND OTHER IMMUNOLOGICAL FUNCTIONS. A SEQUENTIAL STUDY INCLUDING THE INTERACTION OF CORYNEBACTERIUM PARVUM IN MELANOMA PATIENTS.

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Int J Immunopharmacol; 4(3):167-174 1982

The effects of a single dose of phenytoin (PHEN; 300 mg/square meter) upon killer cell (NK) cytotoxicity, serum immunoglobulins, and T and B cell proportions was investigated prospectively in 11 patients (6 males, 5 females) with metastatic malignant melanoma. No acute change in T lymphocyte rosettes, serum immunoglobulins, and DNA synthesis of lymphocyte cultures were observed after PHEN treatment. An early immunosuppression occurred within 10 hr after PHEN with reductions in lymphocyte count and NK activity. This suppression was reversible, with apparent recovery by 58 hr. Such a feature could explain the transient lymphadenopathy observed before cessation of PHEN medication. The profound and early immunosuppression associated with the first PHEN dose was abrogated by Corynebacterium parvum immunization (iv infusion 2 mg/square meter in 300 ml physiological saline over 3 hr) preceding a second dose of PHEN. While the second dose of PHEN caused some immunosuppression, no increase in T cells, NK, and phytohemagglutinin induced cytotoxicity above initial values was observed. (23 Refs)

104. AUGMENTATION OF NATURAL KILLER CELL ACTIVITY AFTER ARTERIAL EMBOLIZATION OF RENAL CARCINOMAS.

Bakke A, Gothlin JH, Haukaas SA, Kalland T

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Cancer Res; 42(9):3880-3883 1982

Preoperative embolization of the renal artery has been reported to improve the survival of patients with advanced renal carcinomas compared to operative treatment only. To investigate possible immunological consequences of tumor embolization, natural killer (NK) cell activity in peripheral blood was investigated immediately before and at different time intervals after occlusion of the renal artery by insertion of a metal coil. A slight increase in NK activity could be observed 24 hr postembolization while a marked augmentation was seen after 48 hr. The high NK activity persisted up to 96 hr after embolization, the last time period included in the study. Two patients undergoing the same procedure but in whom embolization was unsuccessful showed no alteration in NK activity. It is suggested that interferon produced by macrophages activated by the necrotizing tumor might be responsible for the augmentation of NK activity. (Author abstract) (31 Refs)

105. EFFECT OF FATTY ACID MODIFICATION OF CULTURED HEPATOMA CELLS ON SUSCEPTIBILITY TO NATURAL KILLER CELLS.

Yoo TJ, Kuo CY, Spector AA, Denning GM, Floyd R, Whiteaker S, Kim H, Kim J, Abbas M, Budd TW

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Cancer Res; 42(9):3596-3600 1982

Rat hepatoma (Morris 7777) cells modified with either oleic or linoleic acid exhibited greater susceptibility to normal spleen cell-mediated lysis in a 16-hr 51Cr release assay. At effector:target cell ratios of 300:1, the specific lysis of fatty acid-enriched target cells (cultured for 2 days in fatty acid-supplemented medium) by the normal rat spleen cells was 60% higher than the untreated target cells (p less than 0.01). Prolonging the culture in fatty acid-supplemented medium up to 6 days produced similar effects. Analysis of the fatty acid composition of cellular lipids revealed that an elevation of oleic or linoleic acid was the only significant alteration in the hepatoma cells grown in the oleic or linoleic acid-supplemented medium, respectively. The percentage of the acids was increased in the total cellular phospholipids, the choline, ethanolamine, serine, and inositol phosphoglyceride fractions, and the neutral lipids. In conclusion, we suggest that the elevation of oleic acid and linoleic acid contents in the membranes of the fatty acid-modified hepatoma cells may contribute to the increased susceptibility of these cells to natural killer cell-mediated cytotoxicity. (Author abstract) (33 Refs)

106. SENSITIVITY TO ACETYL TYROSINE ETHYL ESTHER INHIBITION OF CELL MEDIATED KILLING DISTINGUISHES FRESHLY ISOLATED NATURAL KILLER (NK) CELLS FROM BOTH IN VITRO ACTIVATED NK CELLS AND T KILLER CELLS (MEETING ABSTRACT).

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Fed Proc; 41(3):415 1982

Low mol wt substrates for chymotrypsin-like proteinases, such as amides and esters of aromatic amino acids, inhibit both human NK activity and mouse T cell killing (CTL). The sensitivity of these two types of cells to inhibition by AcTyrOEt is markedly different. The ID50 for freshly isolated human NK to K562 cells is 0.4 mM, whereas the ID50 for mouse CTL is greater than 3mM. This greater than fivefold difference in sensitivity is not a species difference, as freshly isolated mouse NK cells to YAC targets also have an ID50 of 0.4 mM. Human NK cells activated in vitro by a mixed lymphocyte reaction (MLR), lipopolysaccharide or ethanol require two- to fourfold more AcTyrOEt for inhibition than control cultured cells. However, this difference between these freshly isolated NK cells and in vitro activated NK cells is not a function of events that occur only in culture. Freshly isolated mouse CTL require the same high dose, eg ID50 greater than 3 mM AcTyrOEt, for inhibition as do in vitro secondary MLR CTL. We propose that this difference between endogenous NK and the other cells may be a manifestation of quantitative and/or fundamental differences in the lytic mechanisms utilized by these two cell types. (1 Ref)

107. PEPTIDOGLYCANS EXTRACTED FROM GRAM-POSITIVE BACTERIA - EXPRESSION OF ANTITUMOR ACTIVITY AND STIMULATION OF CYTOTOXIC ACTIVITY OF EFFECTOR CELLS (MEETING ABSTRACT).

Goguel AF, Payelle B, Lespinets G, Nauciel C

I.R.S.C., Villejuif, France

Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

The antitumor effect of peptidoglycans of various structure extracted from different gram positive bacteria was studied on chemically induced fibrosarcomas in mice. Whole expression of activity depends on the route of administration, on the presence of tumor cells injected in admixture with peptidoglycans and on the same peptide moiety structure as the adjuvant activity. The nature of effector cells involved in peptidoglycans-induced tumor resistance was studied. Intraperitoneally injected peptidoglycans increase cytotoxic activity of peritoneal and splenic NK (NC) cells and enhance the generation in the spleen of T cytotoxic cells against an immunizing hybrid tumor cell. These effects were unrelated to the structure of the peptide moiety. Nevertheless peptidoglycans which present antitumor activity also possess the capacity to stimulate B cell proliferation. Antitumor and B mitogenic activities were increased when peptidoglycan were under polymerized form. Thus, it seems likely that the same structure could be necessary in order to induce B cell proliferation and to stimulate some mechanisms of tumor resistance. As all peptidoglycans could stimulate the cytotoxicity of NK (NC) cells and the generation of T cytotoxic cells, it seems that either these cells are not implicated, or that another additional mechanism, yet unknown, is necessary for the expression of antitumor activity of effective peptidoglycans. (no Refs)

108. RESISTANCE OF T LYMPHOCYTE ACTIVATION TO THE TOXIC EFFECTS OF THE ADENOSINE DEAMINASE INHIBITOR, 2-DEOXYCOFORMYCIN (MEETING ABSTRACT).

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Fed Proc; 41(3):603 1982

The effect of the adenosine deaminase (ADA) inhibitor, 2'deoxycoformycin (2'dcf), on the in vitro development of a secondary cytotoxic T lymphocyte (CTL) response to a Gross virus induced lymphoma was studied. When primed spleen cells were co-cultured with tumor cells in the presence of 2'dcf for 5 days, a 50 to 80% reduction in lymphocyte number was observed. However, normal levels of CTL activity were maintained. Immunofluorescence analysis of cells which were destroyed by 2'dcf revealed a 92% reduction of B cells and a 48% reduction of T cells. In spite of this two-fold reduction in T cell content, those T cells which responded to tumor were resistant to the adverse effects of 2'dcf as evidenced by the development of: (1) normal levels of CTL activity, (2) normal numbers of antigen-responsive lymphoblasts, and (3) normal levels of DNA synthesis. These results suggest that T cells undergoing an immune response are resistant to 2'dcf toxicity. Since T cell mitogenesis was also unaffected by 2'dcf, we concluded that resistance to the adverse effects of 2'dcf is a characteristic property of antigen or mitogen activated T lymphocytes. Our results suggest that such resistance is acquired as a consequence of activation. (no Refs)

109. IMMUNOENHANCING ACTIVITY OF NPT 15392: A POTENTIAL IMMUNE RESPONSE MODIFIER.

Merluzzi VJ, Walker MM, Williams N, Susskind B, Hadden JW, Faanes RB

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Int J Immunopharmacol; 4(3):219-224 1982

Effects of NPT 15392 (erythro-9-(2-hydroxy-3-nonyl)hypoxanthine) upon T-cell dependent and independent humoral antibody responses, T-cell mediated cytotoxicity, and hematopoietic progenitor cells were investigated in mice. NPT 15392 enhanced T-cell dependent antibody formation but had no significant effect on T-independent antibody response or clonable B cells. NPT 15392 stimulated the expression of cytotoxic T cells while having no quantitative effect on cytotoxic T lymphocyte (CTL) precursors. No demonstrable effect upon hematopoietic progenitor cells was observed at doses that enhanced immune reactivity. A reduction of colony forming unit megakaryocytes occurred at high doses (3-10 mg/kg). The action of NPT 15392 appeared to be restricted to T-cell dependent immune functions, probably by influencing the interactions of helper T-cells and/or macrophages. Such an interaction may permit maximal differentiation of both T-cell dependent B-cell precursors and CTL precursors to the effector cell stage. (26 Refs)

110. IMMUNOSUPPRESSIVE EFFECTS OF ULTRAVIOLET (280-320 NM) RADIATION AND PSORALEN PLUS ULTRAVIOLET (320-400 NM) RADIATION IN MICE.

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JNCI; 69(1):171-173 1982

Contact hypersensitivity (CHS), a cell-mediated immunologic reaction, can be induced in mice by application of a contact-sensitizing chemical to the shaved skin. Exposing the animals to UV radiation from FS40 sunlamps inhibits the immune response. This inhibition is systemic, since the sensitizer need not be applied to the irradiated site of the animal. The mechanism whereby UV radiation prevents CHS appears to involve the production of suppressor T-lymphocytes. Recent evidence suggests that UV exposure of mice alters the way in which certain antigens are processed, and this altered processing or presentation of antigen results in the activation of the suppressor cell pathway, rather than leading to immunization. Treatment of mice with a photosensitizer, psoralen, plus UV (320-400 nm) radiation also suppresses CHS systemically, but whether the cellular mechanisms are the same as those underlying the suppression from the shorter UV wavelengths remains to be determined. The possible role of these immunosuppressive events in photocarcinogenesis is discussed. (Author abstract) (12 Refs)

THE ROLE OF MACROPHAGES AND MONOCYTES IN THE IMMUNE RESPONSE

111. MONONUCLEAR PHAGOCYTE FUNCTION IN HEAD AND NECK CANCER: NBT-DYE REDUCTION, MATURATION AND MIGRATION OF PERIPHERAL BLOOD MONOCYTES.

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Laryngoscope; 92(7,part1):810-814 1982

The number of blood monocytes, their ability to mature into macrophages, their NBT-dye reduction capacity and their migration towards casein were studied in 29 patients with squamous cell carcinoma of the larynx, 12 patients with squamous cell carcinoma at other sites within the head and neck and two groups of male controls, one of 29.7 yr +-7.2 (SD) and the other of 71.4 yr +-6.8 (SD). An age dependency of monocyte function in healthy individuals was established. Increased numbers of monocytes per ml blood were found in the older men. These cells showed an enhanced migration toward casein. Their maturation capacity was decreased. A clear impairment of migration toward casein was found in the two groups of carcinoma patients. The number of monocytes was only marginally affected. The maturation was found to be enhanced. An impaired recruitment of mononuclear phagocytes at the site of malignant growth due to diminished migratory capacities might be important for failing immune surveillance. (Author abstract) (28 Refs)

112. MACROPHAGE REGULATION OF TUMOR GROWTH.

Courts FJ

The University of North Carolina at Chapel Hill, Chapel Hil, NC

VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary The European Association for Cancer Research; 42(6):2299-B 1981

The studies reported in this work investigate the interactions between macrophages and syngeneic tumor cells and attempt to identify macrophage functional heterogeneity with respect to modulation of tumor cell growth. Initial investigations were undertaken to determine the adequacy of existing methods in evaluating the level of DNA synthesis of tumor cells that were cultured with macrophages. These experiments suggested that macrophages release significant quantities of thymidine in vitro which act as a competitive inhibitor in the traditional tritiated thymidine uptake assay. Other nucleosides were not shown to be released at detectable levels and an assay that utilized tritiated guanosine as a pulse label was developed. This assay was used to determine the level of DNA synthesis in tumor cell targets without the effect of non-radioactive nucleoside inhibitors. Next, the tritiated thymidine release assay, which is commonly used to evaluate tumor cell death mediated by macrophages, was examined. These studies indicated that under wide variety of pulse conditions an internal pool of radiolabelled nucleoside accumulates. With additional time in culture this pool is either incorporated into DNA or is released from the cell. The proliferative state of the tumor cells determined whether label release or incorporation would occur. Macrophages that were shown to inhibit tumor cell division without reduction in viability were found to mediate increased label release. These results suggest that non-cytolytic macrophages may mediate an apparent cytolysis in tumor cells that possess a significant internal pool of labelled nucleoside. These studies also indicated that low level pulses with tritiated thymidine may cause irreparable damage to tumor cell proliferative apparatus. The last group of investigations examined macrophage functional heterogeneity with respect to modulation of tumor growth. (no Refs)

113. SEPARATE REGULATION OF ANTIBODY-DEPENDENT (ADCC) AND NON-SPECIFIC KILLING OF TUMOR TARGETS BY MACROPHAGES: SPECIFIC INDUCTION OF ADCC BY LYMPHOKINE (LK), MICROTUBULE INHIBITORS AND OTHER AGENTS (MEETING ABSTRACT).

Ralph P, Nakoinz I
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Fed Proc; 41(3):802 1982

Adherent resident mouse peritoneal macrophages (M) have low ADCC and oil-induced exudate M have moderate ADCC to B, T and myeloid leukemias in 20 hr (125)IUdR(iododeoxyuridine) release assays. However, both M types can be greatly stimulated by 2 days of pretreatment with LK, certain cytokines, LPS (lipopolysaccharide), phorbol ester (PMA, phorbol 12-myristate 13-acetate), or microtubule inhibitors colchicine, lidocaine or microtubule stabilizer taxol, without inducing nonspecific killing. Microfilament inhibitor cytochalasin B did not stimulate ADCC. ADCC-stimulating factors in LK had a mwt of 60,000 and were separate from M or granulocyte colony-stimulating factors and from MAF (macrophage arming/activating factor) stimulating nonspecific killing of sarcomas. Treatment of M to enhance ADCC caused no effect or a decrease in the ability to kill tumors by nonspecific mechanisms (induced by adding LPS, PMA or LK into the cytotoxic assay). The same results were obtained with 2 cloned M cell lines capable of both ADCC and nonspecific killing. Thus, the two killing mechanisms are regulated separately and are mediated by different and sometimes antithetical states of the M. Monoclonal antibodies to H2, Thy-1 and Ly antigens on lymphoma targets showed that all 4 mouse IgG classes, but not IgM, mediate M ADCC. (no Refs)

114. CYTOTOXICITY OF CANCER PATIENT'S MACROPHAGES FOR TUMOR CELLS.

Cameron DJ, O'Brien P
Dept. Surgery, Medical Univ. South Carolina, 171 Ashley Ave., Charleston, SC, 29403
Cancer; 50(3):498-502 1982

Monocyte derived macrophages were isolated from the peripheral blood of 66 patients with either breast, colon, gynecological or hematological cancers. The macrophages from the breast and gynecologic cancer patients generally did not acquire enhanced cytotoxicity for human tumor cells after incubation with bacterial lipopolysaccharide (LPS). However, when the macrophages isolated from colon and hematologic cancer patients were studied, more than 50% of these patients possessed cytotoxic macrophages. LPS induced macrophage mediated cytotoxicity was also found to be inhibited by factors present in many cancer patient's plasma. Twenty-three of the 50 cancer patients studied possessed a plasma inhibitor capable of suppressing macrophage mediated cytotoxicity by more than 50%. Furthermore, of these 50 patients, 47 were incapable of killing the tumor cells in vitro either because they possessed nonresponsive macrophages and/or they possessed a plasma inhibitory factor. Thus, although macrophage cytotoxic function may be normal in some patients with cancer, cytotoxicity may be inhibited in some patients by factors in autologous plasma thereby rendering the macrophages ineffective in vivo. (Author abstract) (10 Refs)

115. MACROPHAGE MEDIATED TUMORICIDAL ACTIVITY TOWARD MALIGNANT TUMOR VARIANTS (MEETING ABSTRACT).

Huard TK, Kalynych AM, LoBuglio AF
University of Michigan, Ann Arbor, MI, 48109
Fed Proc; 41(3):805 1982

We have examined the capacity of macrophages to kill syngeneic tumor cells that vary in metastatic potential. The capacity of macrophages to kill syngeneic variants of a 3-methylcholanthrene induced fibrosarcoma in normal C57BL/6 mice was assessed in a 3H-thymidine (3-TdR) release assay. The tumor cells used as targets were: a) the parent tumor line that induced tumors in 100% of syngeneic mice and elicited pulmonary metastases in 20-45% of recipients, b) a highly malignant isolate from pulmonary metastases that caused tumors in 100% of recipients and lung nodules in 80% and c) a low malignant cell line adapted for growth in vitro that caused tumors in 25 of recipients and pulmonary lesions in 5%. Since these tumor variants selectively metastasize to the lungs, pulmonary alveolar macrophages (AM) were used as effector cells. The AM were isolated by pulmonary lavage. Cell recovery was 0.4-1.2x10(6) cells/mouse and the cells were greater than or equal to 95% pure by morphology, greater than or equal to 92% nonspecific esterase (+) and greater than or equal to 95% viable. Direct AM cytotoxicity to 1x10(4) 3H-TdR labeled tumor cells was assessed 48, 74 and 96 hr post culture initiation. Preliminary results indicate that AM from normal animals were capable of killing even the highly malignant fibrosarcoma variant. Significant AM cytotoxicity to these malignant variants was observed at effector/target ratios of 1:1 to 10:1. The cytotoxicity increased with time of incubation and was evident against all three malignant variants. (no Refs)

116. MACROPHAGE CYTOTOXICITY MEDIATED BY THE INTERACTION OF REACTIVE OXYGEN SPECIES AND UNSATURATED FATTY ACIDS (MEETING ABSTRACT).

Lazdins JK, Meltzer M
Lab. of Immunobiology, National Cancer Institute National Institutes of Health, Bethesda, MD
9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

Mouse peritoneal macrophages (M) activated in vivo (intraperitoneal infection with Mycobacterium bovis strain BCG (BCG) or in vitro (treatment of sodium caseinate elicited cells with lymphokines (LK)) were cytotoxic to 1023 fibrosarcoma cells. When these M were examined for release of O_2 spontaneously or after triggering with phorbol-12-myristate-13-acetate (PMA), no correlation between tumoricidal activity and release of $O_2^-$was demonstrated. When M were incubated with LK, a time dependent acquisition of tumoricidal activity was demonstrated; nevertheless no increase in either spontaneous or PMA stimulated O_2^-could be detected. Macrophages obtained from mouse strains with genetic defects in M tumoricidal capacity did respond normally for production of O_2^-. When the 1023 fibrosarcoma target cells were examined for their susceptibility to chemically generated H_2O_2 O_2^-or OH a highly non physiological concentration of these toxic molecules was required for killing. The onset of cytotoxic activity is associated with increase of M free cholesterol and percent of unsaturated fatty acids. The role of these molecules in conjunction with the constitutive M property of production of reactive oxygen intermediates was examined. Generation of toxic lipid hydroperoxides from macrophage origin as the toxic molecule is proposed. This model of cytotoxicity was further examined in a cell free O2-generating system. Highly unsaturated fatty acids (linolenic acid C18:3) in the presence of oxygen radicals released from non-cytotoxic macrophages or from chemically generated non-cytotoxic concentration of O2-show a dramatic toxic effect on the examined target cells. (no Refs)

117. STUDIES ON MACROPHAGE KILLING OF TUMOR CELLS (MEETING ABSTRACT).

Zippel D, Fritsch RS
Central Institute of Microbiology and Experimental Therapy, GDR-6900 Jena, W. Germany
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

A macrophage cytotoxicity factor (MCF) rendering BCG-activated mouse macrophages (M) cytotoxic against RAB I tumor target cells in vitro was prepared and chromatographically purified from cell-free fluid of rat Zajdela ascites hepatoma. The interaction of activated M with RAB I tumor cells was investigated by scanning (SEM) and transmission electron microscopy (TEM) after 16 h cocultivation with the cytokine MCF. Sem specimens were prepared by a special method to avoid cell shrinkage. The findings strongly suggest a transport of vesiculated, possibly lysosomal material from M to tumor target cells within special cell protrusions, the nature of which has to be further elucidated by cytochemical studies. (no Refs)

118. POLYRIBOSOME-INDUCED MACROPHAGE-MEDIATED TUMOR CYTOTOXICITY (MEETING ABSTRACT).

Segal W, Urban R
Dept. of Biology, University of Colorado, Boulder, CO
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Specific concentrations of Serratia marcescens polyribosomes (polysomes) directly induced the differentiation of C57Bl/6 murine peritoneal monocytes to cytotoxic macrophages. Cytotoxicity was expressed against syngeneic B16 melanoma target cells, but not against normal syngeneic kidney epithelial cells, in dispersed cultures at effector-target ratios of less than or equal to 2:1. Escherichia coli polyribosomes, E coli endotoxin and Serratia endotoxin did not induce a cytotoxic response. The concentrations of Serratia polysomes that induced tumor cytotoxicity in vitro were identical to those which were previously reported to produce long term survivors in a murine DBA/-SaD2 fibrosarcoma surgical adjuvant model. Polysome preparations were non-reactive in the Limulus amebocyte lysate assay for endotoxin. The addition of polymyxin B to the culture media did not abrogate the in vitro response. Serratia polysomal preparations did not produce dermonecnosis in 4 day-old mice nor did they sensitize 8 week-old CFW mice to histamine. (no Refs)

119. MACROPHAGE-AFFECTING SOLUBLE FACTORS FROM RAT TUMOR ASCITES (MEETING ABSTRACT).

Fahlbusch B, Zachiesche W, Schumann I
Zentralinstitut fur Mikrobiologie und Experimentelle Therapie, Jena, West Germany
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Wistar rats bearing Zajdela ascites hepatoma demonstrated the appearance of soluble factors with the following properties; (1) Inhibition of macrophage migration (MIF); (2) stimulation of macrophage migration; (3) activation of macrophages for reduction of the multiplication of intracellularly growing becteria (MGIF). Kinetic studies showed that the factors appear in the order referred to above. MIF and MGIF present as relatively heat stable (glyco)proteins. They demonstrate striking microheterogeneity with respect to (1) molecular weight as evidenced by gel filtration, (2) net charge as shown by means of ion exchange chromatography, and (3) isoelactric point as shown by isoelectric focussing. There is evidence that the factors are, at least in part, produced by the tumor cells themselves. It may be suggested that factors of the kind referred to above interfere with host defense mechanisms against tumors. (no Refs)

120. TUMOR-BEARING RAT SERUM FACTORS AFFECT NORMAL MACROPHAGE FUNCTIONS. EFFECT OF BACTERIAL ADJUVANTS TREATMENT (MEETING ABSTRACT).

Iannello D, Bonina L, Delfino D, Mastroeni P
Microbiology Institute, Messina, Italy
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Many authors have described depressed macrophage functions in tumor-bearing animals and cancer patients. The deficiency may be related to soluble and dialyzable factors produced by neoplastic cells. In previous experiments we demonstrated defective phagocytic, bactericidal and fungicidal activities of peritoneal macrophages obtained from rats transplanted with an atypical viral epithelioma, T8 of Guerin. Spontaneous migration and chemotactic response were also defective in tumor-bearing animals. These macrophage functions were partially restored with some bacterial adjuvants. In the present paper we describe a depressive effect of tumor-bearing rat serum factor(s) on some normal rat macrophage functions. Moreover, the results obtained by incubating normal rat macrophages with serum of tumor-bearing rats treated with BCG, Corynebacterium parvum or Listeria monocytogenes are described. Results are discussed in terms of possible mechanisms of action of tumor-induced depression of macrophage function and of mechanisms of bacterial adjuvant macrophage activation. (no Refs)

121. MACROPHAGES AND RESISTANCE TO TUMORS. 6. THE EFFECTS OF SUPERNATANTS FROM CULTURES OF NORMAL AND TUMOR CELLS ON PHAGOCYTOSIS.

Nelson M, Nelson DS
Kolling Inst. Medical Res., Royal North Shore Hosp., St. Leonards N.S.W. 2065, Australia
J Reticuloendothel Soc; 31(5):433-450 1982

Mouse resident peritoneal macrophages were cultured with supernatants from cultures of tumor cells and normal cells, then tested for their capacity to phagocytose opsonized sheep erythrocytes (SRBC). Most tumor cells produced inhibitory material but some did not (HeLa, EL-4). Conversely, nonmalignant cells generally did not produce active material though some (Chang B cells) did. Inhibition was not noticeable until after 13 hr contact with tumor supernatant and then became progressively more pronounced at 24 and 48 hr. Phagocytic capacity recovered only partially on reincubation with fresh medium. Inhibition was caused by material of approx MW less than 1,000 (by membrane filtration), which also inhibited macrophage migration in vitro but had no effect on delayed-type hypersensitivity reactions or tumor growth in vivo. There was no species specificity and normal macrophages from various sources were susceptible, although activated or stimulated macrophages were wholly or partly resistant. Tumor carriage was associated with an initial decrease in phagocytic capacity of resident peritoneal macrophages, followed by an increase then a second decrease, although the cells remained susceptible to the inhibitory effect of tumor supernatant in vitro. Depression of phagocytosis was more marked in the presence of normal mouse serum and less marked in the presence of human serum than in the presence of fetal calf serum. Phagocytosis of zymosan and pinocytosis of colloidal gold by mouse macrophages were also depressed by tumor cell products. (Author abstract) (34 Refs)

122. SYNERGISTIC ACTIVATION OF MACROPHAGES BY LYMPHOKINE AND LIPOPOLYSACCHARIDE: EVIDENCE FOR LYMPHOKINE AS THE PRIMER AND INTERFERON AS THE TRIGGER (MEETING ABSTRACT).

Schultz RM
Lilly Research Laboratories, Indianapolis, IN, 46285
Fed Proc; 41(3):845 1982

Murine macrophages can be activated to develop cytotoxicity against P815 mastocytoma tumor cells following incubation in vitro with either bacterial lipopolysaccharide (LPS) or cell-free culture supernatant from mitogen-stimulated BALB/c lymphocytes rich in macrophage activating factor (MAF). Under optimal conditions in an in vitro growth inhibition assay, tumor cytostasis by macrophages treated with MAF or LPS alone did not exceed 30%. The combination of extremely low concentrations of lymphokine (1.25%) with subthreshold amounts of LPS synergistically activated macrophages with greater than 60% inhibition of tumor cell growth. Previous studies have indicated that direct macrophage activation by LPS results via interferon (IFN) induction. Pretreatment of macrophages with subthreshold levels of MAF potentiated the cytotoxicity of macrophages subsequently exposed to interferon. Synergism between MAF and either LPS or IFN required a defined sequence of events. To demonstrate synergism, macrophages had to be either incubated with MAF and the other activating agent simultaneously or treated first with MAF. Thus macrophages exposed to low concentrations of lymphokine supernatants appear to enter into a receptive, primed state in which they are not yet cytotoxic but can be triggered by another signal (LPS or IFN) to develop full cytotoxicity. (no Refs)

123. MACROPHAGE-DERIVED FACTOR REGULATION IN NORMAL AND TUMOR-BEARING HOSTS (MEETING ABSTRACT).

Denbow CJ, Black SP, Conroy JM, Elgert KD
Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, VA, 24061
Fed Proc; 41(3):845 1982

Normal and tumor-bearing host (TBH) BALB/c mouse spleen cell responsiveness to macrophage (M)-derived factors was determined in vitro and in vivo. Mixed lymphocyte reaction (MLR) reactivity of Lyt+ T cell subsets to normal and TBH M supernatant was assessed. TBH M supernatant was less able to enhance lymphocyte subset MLR proliferation than its normal counterpart. Normal M supernatant, injected iv into normal and TBH 24 hr before testing, had no effect on normal spleen cell Con A (concanavalin A)-induced blastogenesis; however, TBH spleen cells exhibited more than a 2-fold increase. No interferon or Interleukin-2 activity was detected in normal or TBH M supernatants, but low levels of Interleukin-1 (IL-1) activity were present. TBH M supernatant contained slightly higher IL-1 activity than normal controls. Prostaglandin (PGE2) concentration was in the range of 10(-9) to 10(-10) M for both normal and TBH M supernatants. PGE2 was titrated in the MLR. A 65% saturated ammonium sulfate (SAS) solution precipitated M-derived inhibitor factors from culture supernatants. Preparative isoelectric focusing further purified the SAS precipitated inhibitory factors with a pI (isolectric point) in the pH 7-8 range. Further purification should delineate if qualitative and/or quantitative differences contribute to tumor-induced immune debilitation. (no Refs)

124. STUDY OF PULMONARY ALVEOLAR MACROPHAGES AND STUDY OF HISTOCHEMICAL MARKERS FOR PULMONARY ALVEOLAR MACROPHAGES AND MACROPHAGES IN BRONCHOGENIC CARCINOMAS (MEETING ABSTRACT).

Soufleris AJ, Pretlow TP, Pretlow TG
University of Alabama in Birmingham, Birmingham, AL, 35294
Fed Proc; 41(3):433 1982

During the course of morphometric studies of stromal cells from human tumors, it became necessary to find markers that would permit the identification of macrophages in tissue sections. Enzyme histochemical methods were applied to 1-2 micron sections of lungs and contiguous bronchogenic carcinomas embedded in plastic. A considerable degree of variability in enzymatic activity was observed among different macrophages and among different patients. The most commonly useful marker for pulmonary alveolar macrophages was alphanaphthyl butyrate esterase; 50-87% of pulmonary alveolar macrophages showed some evidence of this marker histochemically. Pulmonary alveolar macrophages demonstrated evidence of naphthol AS-D chloroacetate esterase in 41-86%, peroxidase in 3-86%, acid phosphatase in 14-100%, and stainable iron in 0-96% of cells. All of these markers were observed in some stromal cells of bronchogenic carcinomas. The lack of any uniformly demonstrable marker enzyme in pulmonary alveolar macrophages suggests that it will be necessary to recognize several subcategories of stromal cells recognized primarily by their observed phenotypic expressions of histochemical markers. (no Refs)

125. INTRA-TUMOR MACROPHAGE HETEROGENEITY: USE OF CENTRIFUGAL ELUTRIATION TO IDENTIFY A TUMOR INFILTRATING ADHERENT CELL WHICH MEDIATES TUMOR GROWTH INHIBITION (MEETING ABSTRACT).

Moore K
Ontario Cancer Treatment and Research Foundation, London, Ontario, Canada
9th International RES Congress, February 7-12, 1982, Davos, Switzerland. American Reticuloendothelial Society 68 pp., 1982.

We have previously demonstrated that the macrophages present within progressively growing solid tumors are heterogeneous. Changes in activation state of a smaller monocyte-like subpopulation are associated with regression of the tumor following intravenous therapy with Corynebacterium Parvum. We now demonstrate that a small adherent cell subpopulation isolated from within a progressively growing methylcholanthrene-induced sarcoma is capable of inhibiting tumor growth in vivo. The Beckman centrifugal elutriator was used to isolate 3 cell fractions from enzyme disaggregated tumor tissue. Fraction I eluting at a higher rotor speed contained 84% lymphocytes with contaminating monocytes and small macrophages, Fraction II contained 93% large vacuolated macrophages and Fraction III 95% tumor cells. These fractions were recombined for subcutaneous injection into syngeneic C3H/HeJ mice. Only cells from Fraction III give rise to tumors. Admixture of 5 x 10(4) fraction I cells with 10(5) fraction III tumor cells completely inhibited tumor growth while macrophages from fraction II were without effect upon tumor growth rate. Removal of the majority of contaminating macrophage/monocyte-like cells from fraction I abrogated this fraction's tumor inhibitory effect. This effector cell falls into the same category as the small, adherent macrophage-like cell we have previously demonstrated to be activated within regressing tumors. The data presented here indicate that cells of this type may be present within progressively growing tumors but they are unable to exert any biological effect until the majority of larger tumor associated macrophages are removed from the tumor inoculum. (2 Refs)

126. NATURALLY OCCURRING CELL-MEDIATED CYTOTOXICITY: AN IN VITRO PHENOMENON DISTINCT FROM THE ANTIBODY-DEPENDENT CELLULAR CYTOTOXIC REACTION (MEETING ABSTRACT).

Banerjee D, Richter MA
Department of Pathology, University of Western Ontario, London, Ontario, Canada
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

Normal circulating human leukocytes consistently lyse rabbit erythrocytes within 24 hours in culture. The effector cell is a C3/Fc receptor-bearing cell with phagocytic properties since specific depletion of C3 receptor-positive, Fc receptor-positive, or phagocytic cells results in a marked decrease in cytotoxic activity. Unlike the antibody-dependent cellular cytotoxic (ADCC) reaction, the cytotoxic reaction in this system (NOCC) requires no specific antitarget cell antibody, cannot be inhibited by the blocking of FC receptors by heat-aggregated gamma-globulin, and is inhibited by fetal bovine serum and by trypsin treatment of the effector cells. The NOCC cytotoxic reaction is dependent upon direct effector-target contact and is not mediated by soluble substances, nor is it mediated through a phagocytic process. (no Refs)

127. A CYTOTOXIC MONOCLONAL ANTIBODY IDENTIFYING AN ANTIGEN PRESENT ON ACTIVATED LYMPHOID CELLS AND TUMORS.

Teplow DB
University of Washington, Seattle, WA
Diss Abstr Int [B]; 42(6):2302-B 1981

Murine cytolytic T lymphocytes (CTL) were injected into semisyngeneic animals. The CTL used were specific for the murine leukemia virus (MuLV)-induced tumor LSTRA. Spleen cells from hyperimmunized animals were fused with NS-1 myeloma cells to produce antibody-secreting hybrids. One hybrid, number 228, produced an antibody capable, in the presence of complement, of abrogating CTL killing in chromium release assays. The species, strain, tissue and cellular distribution of the antigen (Ag 228) defined by this monoclonal antibody were extensively analyzed. Ag 228 is present in large amounts on mitogen-activated T-lymphocytes, syngeneic and allogeneic CTL, mitogen-activated B-lymphocytes and certain leukemias. It is not present at significant levels on resting lymphoid cells, bone marrow cells, testicular cells, fetal cells or a variety of adherent tumor and non-tumor cell lines of human, rat and mouse origin. In vivo data suggest that Ag 228 may play a role, either at the effector cell or target cell level, in the regulation of protective immune responses against tumors. Ag 228 is a non-viral antigen which, in preliminary biochemical studies, appears to be a protein with a molecular weight of approximately 30,000. Its characteristics are similar to those of Ly-19 antigen, non-HLA-DR-related human lymphocyte activation antigens and Ii chains of human, rat and mouse Ia antigens. (no Refs)

128. GENERATION OF LONG-TERM T-LYMPHOID CELL LINES WITH SPECIFIC CYTOTOXIC REACTIVITY FOR A SYNGENEIC MURINE LYMPHOMA.

Eberlein TJ, Rosenstein M, Spiess PJ, Rosenberg SA
NIH, Building 10, Room 10N 116, Bethesda, MD, 20205
JNCI; 69(1):109-116 1982

The long-term in vitro growth in T-cell growth factor (TCGF) of murine cytotoxic T-lymphoid cells directed against syngeneic tumor antigens was investigated. C57BL/6 mice were immunized to syngeneic FBL-3 lymphoma by two ip injections of irradiated FBL-3 lymphoma cells. Splenocytes from these animals were injected into mice with disseminated lethal FLB-3 tumor. The injection of cyclophosphamide (Cy) plus immunized lymphocytes significantly improved survival with cure of 53% of 38 animals. In comparison, treatment with Cy alone resulted in 0 of 31 cured and treatment with Cy plus unimmunized cells resulted in 0 of 40 cured (p less than 0.0005). These in vivo immunized lymphocytes were reexposed to FBL-3 tumor in vitro for 5 days in lectin-free TCGF (LF-TCGF). Although in vivo and in vitro sensitized lymphocytes exhibited no cytotoxicity toward fresh FBL-3 tumor cells in an 18-hour 51Cr release assay, expansion of appropriately sensitized cells in LF-TCGF resulted in significant lysis of fresh FBL-3 tumor cells. This significant lysis was specific and lysed syngeneic FBL-3 but not syngeneic MCA-103 fresh tumor targets. This maximal specific cytotoxicity was maintained for 2.5 months. A screening assay was developed that permitted rapid identification and isolation of low-frequency cytotoxic clones with reactivity specific for FBL-3 tumor. Several of these cloned cells were grown for almost 3 months with maintenance of high degrees of specific lysis (as much as 4,500 lytic U/10(6) cells). These cytotoxic lines and clones will be of value for the study of tumor-host immunologic interactions and perhaps for use in adoptive immunotherapy. (Author abstract) (68 Refs)

RELATED BIOLOGY OF IMMUNE CELLS

129. CT HYBRIDOMAS: TUMOR CELLS CAPABLE OF LYSING VIRALLY INFECTED TARGET CELLS.

Whitaker RB, Kauffman RS, Che M, Finberg R
Dept. Pathology Harvard Medical Sch., Boston, MA, 02115
J Immunol; 129(2):900-903 1982

By fusing primed murine lymphocytes with a syngeneic T cell lymphoma, we have been able to select for H-2-restricted, virus-specific cytotoxic T cell hybridomas (CTH). These T cell hybrids, which replicate in ordinary tissue culture medium or in ascites, are capable of lysing virally infected target cells, and their activity is facilitated by the presence of lectins in the assay medium. Unlike cells mediating lectin nonspecific lysis, these hybridomas are H-2 restricted and specific for single viral proteins. The ability to maintain these cells in culture for over 18 mo and to pass them in vivo without loss of activity or specificity indicates that they will provide sufficient material for the analysis of surface proteins and genetic information required for the recognition and lysis of virally infected cells by killer T cells. (Author abstract) (12 Refs)

130. AN ACCELERATED RECRUITMENT OF CFUC SUBPOPULATIONS AFTER TREATMENT WITH VINBLASTINE.

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Exp Hematol; 10(6):533-543 1982

Granulocyte-macrophage progenitor cells (CFUc) in the bone marrow cells from mice before, and 12 hr to 7 days after intraperitoneal administration of vinblastine (VLB; 4 mg/kg) were serially investigated until Day 14 of culture. The number of CFUc rose to peak levels on Days 7 and 4 of culture in the whole bone marrow cells obtained before and 2 to 4 days after VLB treatment, respectively. A small peak found on Day 11 of culture was marked up to 2 days after VLB treatment when fresh medium containing colony-stimulating factor was added on Day 7. Each CFUc in the bone marrow cells fractionated by velocity sedimentation, counted on Days 4, 7, and 11 of culture, showed distinct subpopulations of varying cell size. There was a correlation between the amount of each CFUc with cellularity and cytodifferential before and after the VLB treatment. Recruitment of stem cells through three CFUc subpopulations in the CFUc compartment is accentuated during convalescence following VLB-induced myelosuppression. (Author abstract) (18 Refs)

131. PRODUCTION OF MACROPHAGE-ACTIVATING FACTOR BY T LYMPHOCYTE CLONES AND CORRELATION WITH OTHER LYMPHOKINE ACTIVITIES.

Kelso A, Glasebrook AL, Kanagawa O, Brunner KT

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J Immunol; 129(2):550-556 1982

The production of macrophage-activating factor (MAF) by antigen-stimulated murine T lymphocyte clones has been compared with their cytolytic function and release of other lymphokines. MAF activity was measured by the capacity of peptone-induced peritoneal exudate cells or bone marrow-derived macrophages to lyse 51Cr-labeled tumor cells after incubation with supernatant from the stimulated T cells and a nonactivating, amplifying dose of lipopolysaccharide. Of 72 clones generated against H-2, Mls, H-Y, or Moloney leukemia virus-associated antigens, 68 were found to produce detectable quantities of MAF. Release of MAF by clones (1) occurred within 1 to 12 hr of exposure to antigen, (2) required stimulation with cells of the relevant antigenic specificity, and (3) could also be induced by concanavalin A, indicating that the cloned cells were the source of the activity. The capacity of a clone to produce MAF was independent of its antigenic specificity, cytolytic activity, or ability to produce interleukin 2 or granulocyte-macrophage colony-stimulating activity. In contrast, production of interferon and MAF was not dissociated for any of the clones tested. (Author abstract) (42 Refs)

132. LACK OF SPECIFICITY FOR VIRAL AND H-2 ANTIGENS BY ANOMALOUS T KILLER CELLS GENERATED IN MURINE LEUKOCYTE CULTURES.

Shain B, Holt CA, Lilly F

Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY, 10461

J Immunol; 129(2):722-729 1982

Mouse spleen cells, cultivated in vitro for 6 days in the presence or absence of syngeneic irradiated virus-induced tumor cells, lysed a variety of virus-induced tumor cells and normal cells in a long (19-hr) 51Cr-release cytotoxicity assay. Little or no specificity for viral or H-2 antigens was detected. This anomalous killing (AK) activity contrasted with H-2-restricted cytotoxic T lymphocyte (CTL) activity generated in secondary mixed leukocyte-tumor cell cultures and detected in a short (4- to 6-hr) 51Cr-release assay. Studies of competitive inhibition by unlabeled target cells in the long assay suggested that AK effectors were a broadly heterogeneous mixture of cells representing many clones, each recognizing a different antigenic determinant. AK effector cells shared properties with CTL: they could be generated from spleen cells of natural killer cell-deficient mice bearing the beige mutation but not from those of T cell-deficient nude mice; they expressed Thy-1 and Lyt-2 antigens; and they were nonphagocytic. AK activity could be generated from normal spleen cells of mice of all inbred strains examined, but the levels of activity generated varied in a strain-specific manner and were not significantly influenced by H-2 genotype. (Author abstract) (50 Refs)

133. STUDIES OF THE CELL LINEAGE OF THE EFFECTOR CELLS THAT SPONTANEOUSLY LYSE HSV-1 INFECTED FIBROBLASTS (NK(HSV-1)).

Lopez C, Kirkpatrick D, Fitzgerald PA, Ching CY, Pahwa RN, Good RA, Smithwick EM

Sloan-Kettering Inst. for Cancer Res., 1275 York Ave., New York, NY, 10021

J Immunol; 129(2):824-828 1982

Natural killer cells that lyse herpes simplex virus-type 1-infected fibroblasts (NK(HSV-1)) have been under study because they are thought to play an important role in host defense against herpesvirus infections. Studies were undertaken of certain patient groups in order to help characterize these cells and develop evidence about the cell lineage to which these effector cells belong. Our studies of bone marrow transplant recipients indicate that this function is derived from bone marrow stem cells. NK(HSV-1) was also found to be dependent on a normal bone marrow, because patients with juvenile osteopetrosis had very low responses. Further, 15 of 17 patients with aplastic anemia (AA) and complete marrow failure also showed very low NK(HSV-1) responses, whereas 9 of 11 AA patients with some evidence of bone marrow precursors had normal responses. Our studies indicate that the NK(HSV-1) effector cells do not belong to the lymphoid lineage of hemopoietic cells. In addition, two severe combined immunodeficiency disease (SCID) patients demonstrated NK(HSV-1) responses without evidence of pre-T cells in their marrow, indicating that these effectors are not pre-T cells. Studies of patients with monocyte/granulocyte lineage dysfunctions were less conclusive. Patients with chronic granulomatous disease and certain SCID patients had normal NK(HSV-1) in spite of dysfunctions of the monocyte/granulocyte series. Although NK(HSV-1) effectors may be related to the precursors of the monocyte/granulocyte series, it is equally possible that these cells belong to an independent hemopoietic cell lineage. (35 Refs)

CMI METHODOLOGY

134. COLONY-FORMING ASSAY FOR CIRCULATING CHRONIC LYMPHOCYTIC LEUKEMIA CELLS.

Taetle R, Richardson D, To D, Royston I, Mendelsohn J
Univ. Hosp. H720, 225 Dickinson St., San Diego, CA, 92103
Leuk Res; 6(3):335-344 1982

Adaptation of a technique for growth of B lymphocyte colonies to peripheral blood cells of 18 patients with clinically and pathologically typical chronic lymphocytic leukemia (CLL) is reported. T-lymphocyte-depleted CLL peripheral blood cells were cultured with irradiated, normal T cells, and media conditioned by normal, mitogen-stimulated T cells in methylcellulose. Small colonies of approx 40 cells appeared after 5-7 days incubation and little or no growth was noted in the absence of irradiated T lymphocytes. The relationship between the number of cells plated and number of colonies observed was linear over a wide range of plating concentrations. No correlation was observed between plating efficiency and the number of circulating leukocytes or lymphocytes. A high percentage of CLL colony-forming cells were synthesizing DNA (S phase). Cells harvested from normal T lymphocyte colonies were greater than 95% sheep red blood cell-rosette positive and greater than 95% positive when stained for OKT3 and/or T101, compared with less than 5% of cells harvested from CLL colonies. The presence of large numbers of surface immunoglobulin positive cells could not be demonstrated in CLL colonies. Drug sensitivity studies to adriamycin (ADM) and melphalan (ME) were performed on five patients previously treated with alkylating agents and five patients who were untreated. CLL colony-forming cells were relatively resistant to ADM, although untreated patients were less resistant than previously treated ones. Previously treated patients were also relatively resistant to ME. Results indicated that the reported system can be used to study regulation of CLL cell proliferation, and may have utility in predicting response to chemotherapeutic agents. (37 Refs)

135. MONOCLONAL ANTIBODIES AND T-CELL HYBRIDOMAS. PERSPECTIVES AND TECHNICAL ADVANCES.

Hammerling GJ, Hammerling U, Kearney JF
Institut fur Immunologie und Genetik, Deutsches Krebsvorschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Monoclonal Antibodies and T-Cell Hybridomas. Perspectives and Technical Advances. Amsterdam, Elsevier/North-Holland Biomedical Press, Research Monographs in Immunology, Vol. 3, 587 pp., 1981.

Production of monoclonal antibodies to a wide range of antigens including antigens of the major histocompatibility complex of man and rodents, as well as other tissue antigens is presented. Reagents to detect and react with antigens from human tumors are described. Monoclonal antibodies to tissues other than those involved in neoplastic transformation are discussed. The use of monoclonal antibodies in the diagnosis of infectious diseases, particularly parasitic disease, is presented as are monoclonal antibodies to allergens and hormones. The use of monoclonal antibodies in analyzing immunological phenomena themselves, particularly aspects of idiotypic expression and interactions is discussed. The production of monoclonal antibodies by human hybridomas is described. T-cell hybridomas are a major advance in research of T-cell function and make T-cell products, both helper and suppressor factors, available for study. A practical guide for the derivation of antigen-specific hybridoma lines is provided. Human tumor-associated antigens are discussed with respect to those associated with solid tumors and melanomas, soluble products of tumors, and antibody-mediated tumor therapy. (1236 Refs)

136. CRYOPRESERVATION OF HUMAN PERIPHERAL BLOOD LYMPHOID CELLS REACTIVE TO ALLOGENEIC ANTIGENS, VIRUS-TRANSFORMED AUTOLOGOUS CELLS AND AUTOLOGOUS LEUKEMIA CELLS IN IN VITRO SENSITIZATION.

Yamada H, Kodera Y, Yamada K
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, Nagoya, Japan
Nagoya J Med Sci; 44(3/4):117-131 1982

The ability of cryopreserved human peripheral blood lymphocytes (PBLs) to respond to Epstein-Barr virus (EBV)-transformed autologous cells, autologous leukemia cells, and allogeneic lymphocytes was studied with the use of a micro method for determination of in vitro sensitization which allows serial dilution of the responding cells. The 51Cr release assay was used to determine cell-mediated cytotoxicity. After 7 days in vitro sensitization with alloantigens, maximal cytotoxicity was obtained at an equivalent level in cryopreserved and fresh PBLs. In 5/6 experiments, cytotoxicity generated from cryopreserved PBLs reached maximal levels equivalent to those of fresh PBL at the same or one-fold different numbers of responding cells. Use of either EBV-transformed autologous cells or autologous leukemia cells for in vitro sensitization produced approx the same cytotoxicity response whether cryopreserved or fresh PBLs were used. In 2/5 experiments with in vitro sensitization of the PBLs of a 36-yr-old patient with acute myelogenous leukemia against his own leukemia cells, his PBLs reacted to his leukemia cells without addition of an immune modulator in vitro. This activity was lost when cryopreserved PBLs were used, but when the PBLs were co-incubated with his autologous leukemia cells in the presence of Nocardia rubra cell wall skeleton (N-CWS) for 7 days, the cytotoxicity on autologous leukemia target cells reappeared. Removal of N-CWS just prior to assay did not change the outcome of the assay. (15 Refs)

137. PURIFICATION OF HUMAN BONE MARROW (BM) CELLS PRIOR TO TRANSPLANTATION (MEETING ABSTRACT).

Vriesendorp H, Gordon LI, Kies MS, Kucuk O, Prachand S, Visser T
Northwestern University, Chicago, IL, 60611
Proc Am Soc Clin Oncol; 1:C-734 1982

Human BM cells were separated into four fractions using a discontinous bovine albumin gradient in an effort to concentrate hemopoietic stem cells and remove T lymphocytes or tumor cells. BM was obtained from 35 normal human volunteers, 3 patients (pts) with multiple myeloma (MM), 2 pts with small cell carcinoma of the lung (SCCL) and 3 pts with metastatic breast carcinoma (BC). BM fractions were analyzed for granulocyte-macrophage colony forming units (CFUc), tumor colony forming units (TFUc), phytohemagglutinin (PHA) response and rosette formation with sheep erythrocytes (SRBC). A 9 fold increase in CFU concentration and over 75% of total CFUc were found in low density fraction 3, which also was PHA negative and contained 20% of the total number of SRBC rosette forming cells. After conditioning with radiation and cyclophosphamide, engraftment was obtained in two patients with chemotherapy resistant acute leukemia with 3 x 10(7) cells/kg body weight from fraction 3. No prophylactic methotrexate was given. Histological signs of moderate graft-vs-host disease were observed within a month after BMT. In further experiments with normal human BM additional T lymphocyte removal was obtained by rosetting fraction 3 cells with SRBC. The non-rosetting fraction contained 80-100% of the total CFUc and less than 1% of the total rosette forming cells. In cancer pts BM TCFUc were isolated primarily in heavier fraction 4 in MM or lighter fraction 1 + 2 in SCCL and BC while CFUc remained in fraction 3. (no Refs)

SUPPRESSOR CELL ACTIVITY

138. SUPPRESSOR CELL ACTIVITY IN PERIPHERAL BLOOD OF PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE TONSIL.

Mang W, Hammer C, Landauer I, Gruber F
Ear, Nose, Throat Clinics, Ludwig-Maximillians-Universitat, Munich, W. Germany
Excerpta Med Int Congr Ser; 582:249-253 1982

The suppressive activity of mononuclear cells in 62 patients with squamous cell carcinoma of the tonsil was investigated. Patients were treated with surgery plus irradiation, irradiation alone, or irradiation plus chemotherapy. Two tests were used as indicator systems: the phytohemagglutinin stimulated culture, and the one-way mixed lymphocyte reaction. Suppressor activity (SA) of peripheral blood lymphocytes of healthy controls was approx 20%. SA was similar in patients treated by surgery prior to surgery and increased after surgery. Similar findings were reported after irradiation. However, after chemotherapy, SA fell from approx 40% to approx 10%, reflecting the immunosuppressive activity of the chemotherapy. Total SA of activated and spontaneous suppressor cells fluctuated around normal values. SA was low in patients showing no signs of disease and high in patients with growing tumors. SA was high in patients with inoperable disease, decreased and fluctuated over the next 12 mo, then reached a max at 14 mo. SA in lymph nodes was always higher than that in peripheral blood. Lymph node lymphocytes showed a marked increase in SA when tested in allogenic blast formation, suggesting a direct effect of the tumor on suppressor cell population. No correlation of SA with tumor stage could be found. (no Refs)

139. SUPPRESSOR CELLS IN TUMOR PROGRESSOR AND REGRESSOR RATS (MEETING ABSTRACT).

Hollingsworth MA, Hogan KT, Evans DL
Bowman Gray School of Medicine, Winston-Salem, NC, 27103
Fed Proc; 41(3):413 1982

Unfractionated (UNF), nylon wool nonadherent (NA), and nylon wool adherent (ADH) spleen cells from New Zealand Black rats (NBR) bearing progressively growing methylcholanthrene induced fibrosarcomas (MCA) are unresponsive to stimulation with Con-A (concanavalin A), PHA (phytohemagglutinin), and irradiated MCA tumor cells. Equivalent fractions from MCA tumor regressors respond to Con-A, PHA, and MCA stimulation. All cell fractions (UNF, NA, and ADH) from progressors suppress normal spleen cell proliferative responses (in reconstitution assays) to Con-A, PHA, and MCA. Similar to progressor ADH cells, regressor ADH cells suppress the normal Con-A and PHA response in reconstitution assays. In contrast, NA and ADH cells (when reconstituted) enhance the normal response to MCA stimulation. Density gradient centrifugation of progressor NA or ADH cells through linear (0-90%) Percoll gradients produced suppressor activity from cells which had previously been shown to respond to Con-A, PHA, and MCA tumor cells. Indomethacin treatment (10(-4) to 10(-7) M) did not restore responsiveness in progressor cels, nor did it eliminate suppression in reconstitutions with normal cells (ie suppression was not prostaglandin mediated). The difference in progressor and regressor rats implies that at least two suppressor activities may be relevant to the tumor immune status of the rat. (no Refs)

140. FUNCTIONAL PROPERTIES OF UV1: A CONTINUOUS T-SUPPRESSOR CELL LINE WITH TUMOR SPECIFICITY (MEETING ABSTRACT).

Roberts LK, Spellman CW, Warner NL
Department of Pathology, University New Mexico School of Medicine, Albuquerque, NM, 87131
Fed Proc; 41(3):478 1982

A continuous T-suppressor cell line (UV1) has been derived from a Balb/c mouse irradiated with a subcarcinogenic dose of ultraviolet light (UV). UV1 was established by placing nylon wool non-adherent splenocytes directly into tissue culture, supplemented with interleukin 2, without exogenous antigenic stimulation. This cell line has been cloned and maintained in exponential growth culture for approximately 10 months. UV1 expresses a number of T-cell antigens, including Thy 1.2, and is negative for various B-cell and macrophage markers, as well as Lyt, 1, 2 and 3, by FACS analysis. Functionally, UV1 injected either intravenously or intraperitoneally renders mice susceptible to the growth of UV-regressor tumors. These tumors are rejected when implanted into normal syngeneic hosts that lack a state of UV-induced tumor-specific suppression. UV1 also enhances the growth rate of UV-progressor tumors. In addition to its in vivo activity, UV1 is also capable of in vitro function. Cytotoxic T-lymphocytes (CTL) differentiate after 4 days in tissue culture from the draining lymph nodes (DLN) of UV-tumor immune mice. This CTL conversion can be effectively blocked by co-incubating DLN cells with UV1. It appears that UV1 has functional specificity for common tumor associated antigens. This continuous cell line will now allow us to study various host-tumor interactions that result in either tumor growth or rejection. (no Refs)

141. ABROGATION OF THE IN VITRO GENERATION OF THE CYTOTOXIC T-CELL RESPONSE TO A MURINE TUMOR: THE ROLE OF SUPPRESSOR CELLS.

Frost P, Prete P, Kerbel R
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Int J Cancer; 30(2):211-217 1982

A reproducible in vitro assay for the effect of suppressor T cells on the generation of an in vitro cytotoxic response to a metastatic murine tumor is described. Suppression in this system is maximal. The model uses splenic T cells from DBA/2 mice bearing the MDAY-D2 metastatic tumor as suppressors of the in vitro generation of a cell mediated cytotoxic response by syngeneic tumor-bearer (ie, primed) peripheral lymph node cells stimulated with mitomycin C-treated MDAY-D2 tumor cells. The effect of the cell mediated cytotoxic response is profound, specific and mediated by splenic T cells. The suppressor T cells appear to impair precursor rather than mature cytotoxic cells. A highly immunogenic variant of MDAY-D2, namely MDW1, does not generate a suppressor response. Suppressor T cells from an MDAY-D2 tumor-bearer cannot suppress the in vitro response to MDW1. This model of potent suppressor T-cell action is highly reproducible and offers an opportunity for the analysis of why some tumors generate an effective cell mediated cytotoxic response while others stimulate dramatic suppressor T-cell response. (Author abstract) (16 Refs)

142. RADIATION-INDUCED MOUSE CHIMERAS: A CELLULAR ANALYSIS OF THE MAJOR LYMPHOID COMPARTMENTS, FACTORS AFFECTING LETHAL GRAFT VERSUS HOST DISEASE AND HOST-TUMOR INTERACTIONS.

Rudolph A
The George Washington University, Washington, DC
Diss Abstr Int [B]; 42(10):3951-B 1982

The role of suppressor cell elimination in resisting tumor growth was investigated using radiation induced mouse chimeras. Methods reported for selectively eliminating these suppressor cells inhibited the growth of a methylcholanthrene induced sarcomas in these chimeras but further experiments failed to demonstrate that this resistance was specifically due to the selective elimination of suppressor cells. Instead, local effects of irradiation alone at the site of tumor inoculation could account for this lack of growth. (no Refs)

OTHER RELATED STUDIES

143. USE OF YOUNG NUDE MICE FOR SELECTION OF SUBPOPULATIONS OF CELLS WITH INCREASED METASTATIC POTENTIAL FROM NONSYNGENEIC NEOPLASMS.

Pollack VA, Fidler IJ
(c/o Fidler) Cancer Metastasis and Treatment Lab., NCI-Frederick Cancer Res. Facility, P.0. Box B, Frederick, MD, 21701
JNCI; 69(1):137-141 1982

The purpose of these studies was to investigate whether young (3-wk-old) nude mice, which lack functional T-lymphocytes and demonstrate low natural killer cell activity, could serve as in vivo models for the selection of metastatic subpopulations of cells from heterogeneous allogeneic melanomas. Three-wk-old BALB/cAnN or N:NIH(S) nude mice received iv injections of single cells harvested from either the B16 or K-1735 melanoma. Individual pulmonary metastases were harvested 4 wk later and implanted sc into nude mice to expand the population. Cells from each of these metastases colonized in the lungs of 3-wk-old nude mice and 6-wk-old normal syngeneic mice with significantly higher efficiency than did cells from the parent tumors. It was concluded that, in addition to being a useful in vivo model for ascertaining the metastatic potential of neoplasms, the healthy young nude mouse could be used for selecting and maintaining tumor cell variants of high metastatic potential from heterogeneous allogeneic tumors. (Author abstract) (33 Refs)

144. THE MECHANISM OF LITHIUM CARBONATE-INDUCED AUGMENTATION OF COLONY-STIMULATING ACTIVITY ELABORATION IN MAN.

Verma DS, Johnston DA, Spitzer G, Zander AR, Dicke KA, McCredie KB
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Leuk Res; 6(3):349-363 1982

The effects of lithium on monocyte macrophage- and T-lymphocyte-derived colony-stimulating activity (CSA) were studied in vitro to investigate the reasons for the variability of Li stimulation of CSA production by various cell populations from different donors and to delineate the mechanisms involved in Li-augmented granulopoiesis. Results suggested that Li directly stimulated both monocyte-macrophage- and T-lymphocyte-CSA production and that the increase was related to the Li dose and the blood donor used. (44 Refs)

145. CURRENT CONCEPTS ABOUT THE PATHOGENESIS OF SILICOSIS AND ASBESTOSIS.

deShazo RD
Clinical Immunology Section, Tulane Univ. Sch. Medicine, 1700 Perdido St., New Orleans, LA, 70112
J Allergy Clin Immunol; 70(1):41-49 1982

Silicosis and asbestosis are two forms of fibrotic lung disease resulting from the inhalation of inert materials indigestible by pulmonary alveolar macrophages. Results of studies of the host response to these particulates have not always been consistent. It is clear, however, that after phagocytosis, both cause alveolar macrophage damage, with resultant release of macrophage products, including fibrogenic factors and chemotactic factors for neutrophils. The latter cells also release lysosomal enzymes and free radicals when exposed to silica and asbestos. The net effect of these observations suggests that the combination of tissue damage and fibroblast stimulation results in the pulmonary fibrosis characterizing these diseases. Patients with silicosis and asbestosis have normal or decreased cell-mediated and increased humoral immunity with a high incidence of circulating immune complexes and autoantibodies. Whether these abnormalities are related to the pathogenesis of pulmonary fibrosis or are epiphenomena remains to be determined. (Author abstract) (66 Refs)

146. THE MODULATION OF STEM CELLS BY DOXORUBICIN (AM) AND VINBLASTINE (VNBL): A COMPARISON (MEETING ABSTRACT).

Orsini F, Williams D, Fitzpatrick J
Roswell Park Memorial Institute, Buffalo, NY, 14263
Fed Proc; 41(3):813 1982

AM and VNBL have been shown to modulate the immune response. The present investigation was initiated to determine whether the effect(s) of these drugs was at the pluripotent and/or committed stem cell level(s). Two assays were used: 1) The 51Cr release cytotoxicity assay for CMI, (cell mediated immunity), and 2) A double layer agar technique for granulocyte-macrophage (G-M) colonies. In order to determine drug effects on G-M colonies and CMI, inbred C57BL/6 mice were injected with equitoxic doses of AM or VNBL. On days 1,3,5, and 7 after drug administration mice were killed and bone marrow (B) and splenic (S) G-M colonies were assessed in vitro. In addition, S cells were mixed on day 0 with X-irradiated P815 cells. The primary CMI response was tested at its day 4 peak by measuring the percent specific release of 51Cr, from prela-

beled P815 cells, caused by the sensitized cells. It was found that both CMI and G-M colonies from AM treated mice were greatly increased. In comparison VNBL increased B and S colonies 350 and 5000 percent of control, respectively. However, VNBL suppressed the development of the CMI response. These data indicate that AM may possibly modulate non-committed stem cells. In contrast, the primary enhancing action of VNBL is more likely active at the committed stem cell level; since VNBL did not enhance both CMI and G-M colonies, as was the case with AM. (no Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Abai AM 42
Abbas M 105
Alexandrov I 58
Alfred LJ 5
Altman LC 79
Ambrosius H 26
Anzil AP 51
Arena A 65
Bagasra O 74
Bakke A 104
Bakke A 18
Balm FJ 111
Banerjee D 126
Bartlett GL 54
Bartocci A 96
Bash JA 83
Begin R 38
Behrens K 3
Beladi I 31
Beladi I 80
Bell M 55
Benczur M 17
Benczur M 24
Benczur M 80
Bennett M 101
Berdel WE 59
Berlinger NT 1
Bernstein ID 89
Bertotto A 28
Bhatti RA 41
Bilzer T 51
Black SP 123
Blomgren H 6
Bloom BR 68
Boeva M 45
Bolanca S 11
Bonina L 120
Bonina L 65
Boon T 48
Boyer CM 54
Bracaglia AM 28
Bradley C 5
Broccia G 8
Brooks CG 66
Brunner KT 131
Budd TW 105
Cabirac G 61
Caignard A 84
Cameron DJ 114
Carroll PG 90
Catalona WJ 76
Catovsky D 14
Cengiacott L 8
Cernetti C 28
Che M 129
Chiang T 53
Ching CY 133
Chirigos MA 96
Choremi H 15
Cianciolo G 35
Cohen SA 70
Collins JJ 75
Colot M 20
Conroy JM 123
Constandinidou 15
Constantoulakis 15
Corbeil LB 61
Courts FJ 112
Crowther D 103
Cupisol D 87
Czupryna A 22
Dahme E 51
Damjanov I 74
Davigny M 56
Davis S 28
De Mulder P 36
De Pauw B 36
DeShazo RD 145
Del Giacco GS 8
Delfino D 120
Denbow CJ 123
Denning GM 105
Deodhar S 53
Devereux DF 75
Dewolf WC 90
Di Tucci A 8
Dicke KA 144
Dickinson AM 19
Dombernowsky P 34
Donner L 32
Dontchev T 45
Drexhage HA 111
Eberlein TJ 128
Eberlein TJ 91
Economidou J 15
Ehrke MJ 94
Elgert KD 123
Elion GB 92
Esteve C 87
Evans DL 139
Evans DL 86
Evans R 77
Faanes RB 109
Fahlbusch B 119
Falini B 28
Favier F 87
Fekete B 42
Fekete B 44
Fidler IJ 143
Filchev A 57
Finberg R 129
Fisa M 99
Fitzgerald PA 133
Fitzgerald PA 78
Fitzpatrick J 146
Florentin I 56
Floyd R 105
Foa R 14
Ford RJ 39
Fredrickson GG 101
Fritsch RS 117
Frost P 141
Fudenberg HH 72
Fuhrman SA 71
Furcht LT 82
Galton DA 14
Garam T 24
Geerling J 43
Gengozian N 100
George S 19
Gilbertsen B 60
Gill G 5
Gindl P 26
Glasebrook AL 131
Glasgow LA 81
Gnagy MJ 72
Goguel AF 107
Good RA 133
Gordon LI 137
Gorog G 80
Gothlin JH 104
Gothlin JH 18
Gotz J 25
Graubner M 25
Grimm EA 91
Gruber F 138
Guinan PD 41
Gunn H 95
Haanen C 36
Hadden JW 109
Hadden JW 56
Hadjikirove M 45
Haglid KG 51
Haim N 10
Hammer C 138
Hammerling GJ 135
Hammerling U 135
Harris DT 86
Haukaas SA 104
Haukaas SA 18
Hausner P 32
Heidloff M 25
Henney CS 66
Herlyn D 85
Herrmann F 13
Herzog B 88
Higginson K 21
Hill SA 23
Hiraoka A 130
Hoffmann G 33
Hogan KT 139
Hogan KT 86
Hollan Zs 80
Hollingsworth M 139
Holt CA 132
Huard TK 115
Hudig D 106
Hulten M 51
Iannello D 120
Iannello D 65
Indiveri F 8
Jacob HS 82
Jacobs E 19
Jakimov M 58
Jankovic BD 47
Jauer B 13
Jeannin JF 84
Jira M 99

Johnston DA 144
Jones DB 21
Kadagidze ZG 12
Kalland T 104
Kalland T 18
Kalynych AM 115
Kamamoto T 130
Kanagawa O 131
Kaplan HS 9
Kasuga M 37
Katz IR 55
Kauffman RS 129
Kawase I 66
Kay NE 82
Kearney JF 135
Kelsey DK 81
Kelso A 131
Kerbel R 141
Khin W 41
Kies MS 137
Kikuchi K 23
Kim H 105
Kim J 105
Kirkpatrick D 133
Klener P 32
Klimovich VB 49
Klimpel GR 79
Kodera Y 136
Kofina A 15
Kojima O 37
Konjevic G 16
Koprowski H 85
Kosak KM 81
Kotb M 108
Kotnik V 88
Kovesi G 44
Krajina Z 11
Kreider JW 54
Kripke ML 110
Krivec V 88
Kucuk O 137
Kumar RK 46
Kuo CY 105
Kurimoto T 37
Ladusch M 26
Landauer I 138
Lang I 95
Laughter AH 39
Lauria F 14
Lazdins JK 116
Leclerc A 84
Lee FH 52
Leibowitz J 61
Lemaire G 97
Lemaire I 38
Lepoivre M 97
Lespinets G 107
Levin FC 63
Levin J 63
Lilly F 132
Littmann M 26
LoBuglio AF 115
Locci F 8
Lochner A 13
Longley RE 98
Lopez C 133
Lopez C 78
Lotze MT 91
Lydyard P 95
Maca RD 102
Mace K 94
Majima S 37
Makhonova LA 12
Mandal AK 5
Mang W 138
Mantovani G 8
Martelli MF 28
Martin F 84
Masse S 38
Mastroeni P 120
Mastroeni P 65
Mathe G 56
Mathieu A 8
Matzku S 67
Mayakova SA 12
Mazumder A 91
McAdam KP 71
McCarthy J 82
McCredie KB 144
Medzihradsky J 92
Meidav A 10
Meltzer M 116
Mendelsohn j 134
Merendino A 65
Merluzzi VJ 109
Meuret G 33
Mickshe M 20
Mier P 36
Mihich E 94
Minassian AA 29
Minning L 106
Molinari JA 73
Moore K 125
Mule JJ 62
Munder P 59
Munson D 69
Mytar B 22
Mytar B 7
Nagubadi SR 41
Nakoinz I 113
Nauciel C 107
Nelson DS 121
Nelson M 121
Neuwelt EA 23
Nielsen H 34
Nikiforakis E 15
Nishioka B 37
Nolan JP 70
O'Brien P 114
Oakley DM 76
Ohkubo T 130
Olsson O 84
Onody K 80
Oosterhuis JW 74
Orsini F 146
Pahwa RN 133
Panje WR 102
Papademetriou V 96
Papajannis A 15
Parkinson DR 69
Parkinson DR 71
Payelle B 107
Perri RT 82
Peterman GM 79
Petit JF 97
Petranyi GG 24
Petranyi Gy 80
Petrini B 6
Pettersson T 27
Philippen H 13
Phillip MJ 73
Pollack VA 143
Popiela T 7
Prachand S 137
Prete P 141
Pretlow TG 124
Pretlow TP 124
Price JA 93
Proctor SJ 19
Pulay T 24
Pulay TA 17
Quinn RP 92
Rager-Zisman B 68
Ralph P 113
Rambotti P 28
Ratliff TL 76
Read EL 96
Redelman D 106
Reimann S 26
Rey A 87
Rice L 39
Richardson D 134
Richardson M 5
Richter MA 126
Roberts LK 140
Robinson E 10
Robinson E 83
Roed-Petersen B 40
Rola-Pleszczyns 38
Rosenberg SA 128
Rosenberg SA 91
Rosenstein M 128
Rosenstein M 91
Rossi RM 100
Royston I 134
Rubin RH 30
Rucheton M 87
Rudolph A 142
Ruggiero I 7
Ruhl H 13
Ryoyama K 94
Salazar D 70
Samoilovich MP 49
Samuelly B 10
Schaffner H 26
Schlick E 96
Schmitt E 33
Schultz RM 122
Schumann I 119
Schutt A 3
Segal R 10
Segal W 118
Sell S 61
Serrou B 87
Sesterhenn K 3
Shain B 132
Shao-hsien C 95
Shapiro A 76
Sirois P 38
Skaletsky E 61
Smith RE 93
Smithwick EM 133
Snow GB 111

Sonis ST 75
Sorokin EN 29
Soufleris AJ 124
Spector AA 105
Spellman CW 140
Spiess PJ 128
Spinozzi F 28
Spitzer G 144
Stanton GJ 79
Stavrou D 51
Strayer DS 61
Strejcek J 99
Stutman O 50
Suhajova E 99
Susskind B 109
Susuleva NA 12
Swindell R 103
Synderman B 35
Szabo J 24
Tabagari DZ 12
Taetle R 134
Taki M 2
Taylor E 56
Tenu JP 97
Teplow DB 127
Thatcher N 103
Thorbecke GJ 55
Tilney NL 75
To D 134
Toth M 80
Trifonov S 57
Trifonov S 58
Tsang KY 72
Twomey JJ 39
Uchida A 20
Uchino H 130
Uehara Y 37
Ullmann L 26
Uracz W 22
Uracz W 7
Urban R 118
Urdal DL 66
Urso P 100
Vajnstangl M 47
Van Pel A 48
Van Rennes H 36
Varga M 17
Veit BC 108
Velardi A 28
Venkatesan N 5
Verma DS 144
Vessella RL 82
Visser T 137
Vogel D 83
Von Blomberg ME 111
Von Wussow P 78
Vose BM 4
Vozelju M 88
Vriesendorp H 137
Wagener D 36
Waksal SD 69
Waksal SD 71
Waldermann F 33
Walker MM 109
Wan HH 103
Warner NL 140
Wasserman J 6
Watanabe S 37
Wathen LM 64
Weber TH 27
Welin MG 27
Welker RD 96
Whitaker RB 129
Whiteaker S 105
Wilkinson PM 103
Williams C 5
Williams D 146
Williams N 109
Wolberg G 92
Wright DH 21
Yamada H 136
Yamada K 136
Yamagishi M 130
Yamane T 37
Yeager AM 63
Yen-Lieberman B 53
Yoo TJ 105
Yoshida Y 130
Young LS 30
Yu AS 89
Zander AR 144
Zanker KS 51
Zembala M 22
Zembala M 7
Zhogoleva IB 12
Zippel D 117
Zoller M 67
Zschiesche W 119

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